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DISEASES

of the

CHEST

OFFICIAL PUBLICATION

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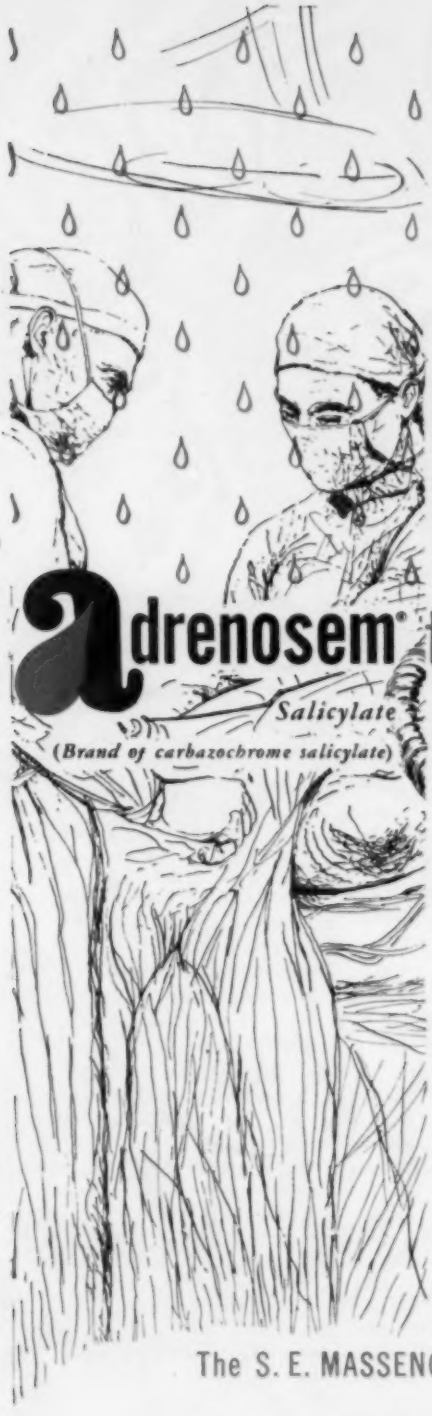

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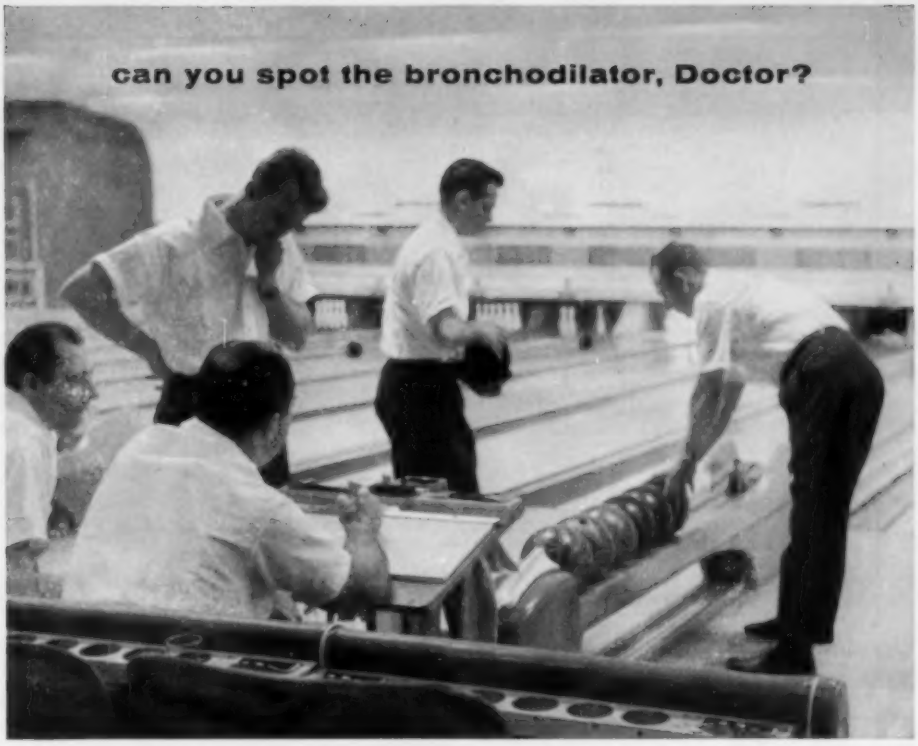

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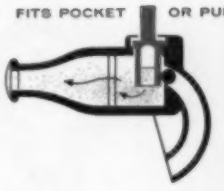

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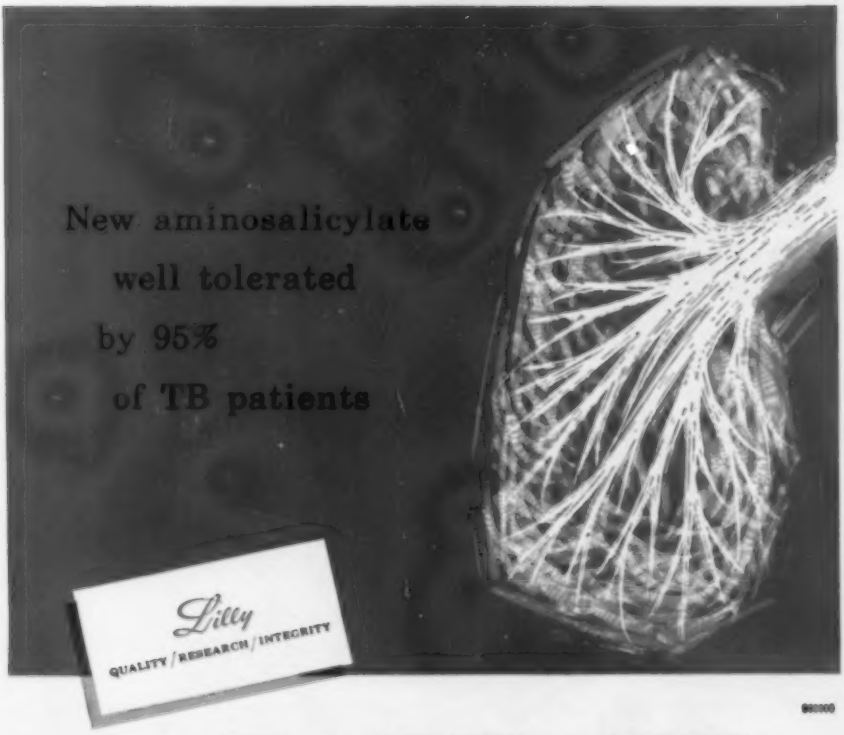

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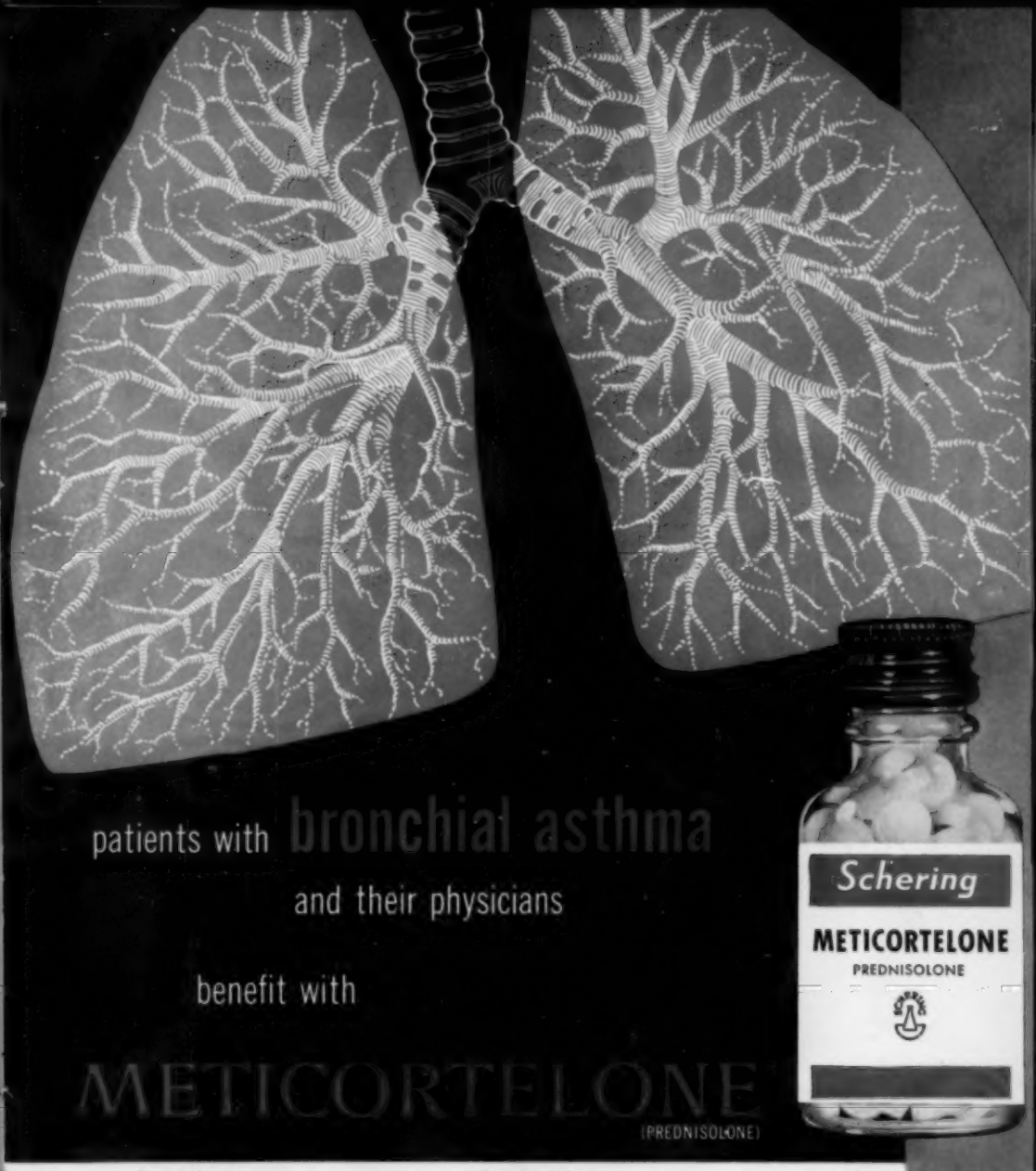

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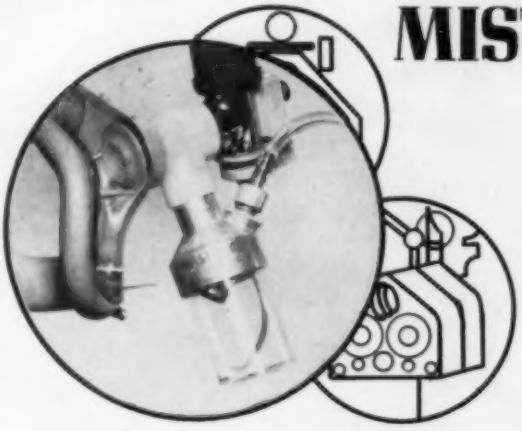

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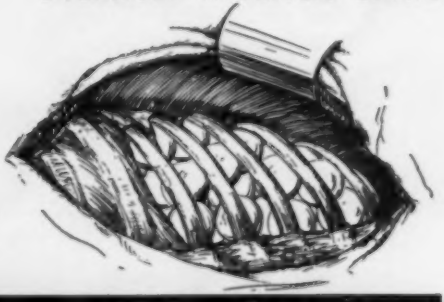

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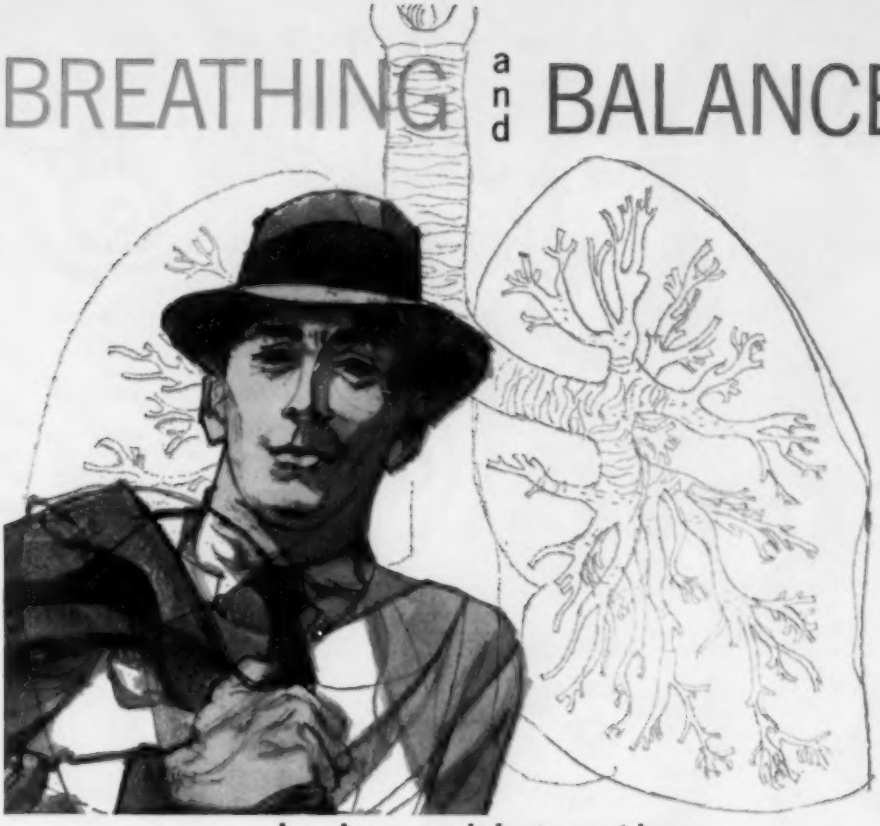

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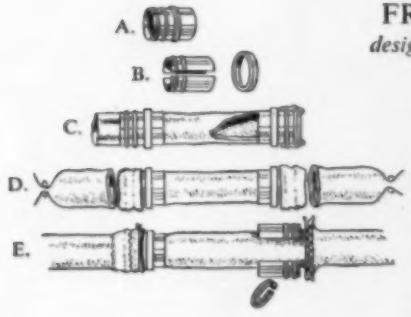

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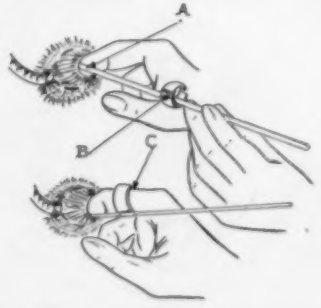

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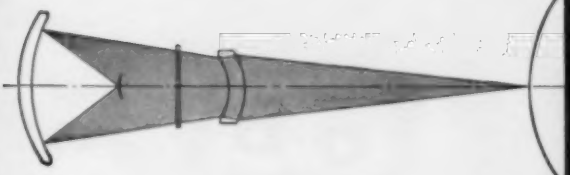

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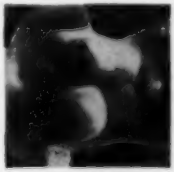

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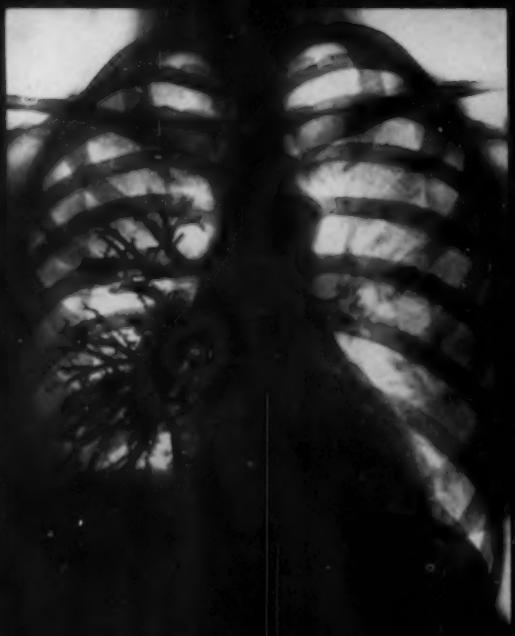
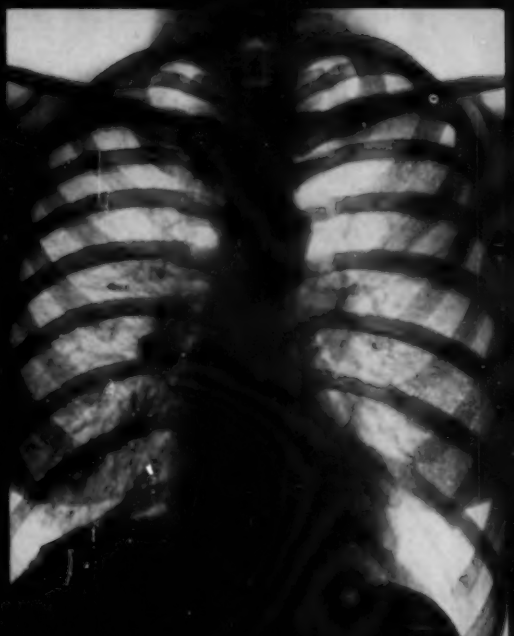


Bronchogram of right lung with VISCIODOL. Note clear outline of bronchi and absence of alveolar filling.



Chest x-ray three days after bronchogram. Note clearing of VISCIODOL and fluid level in right hilar cavity.

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1. Burrascano, J. J.: Sea View Hosp. Bull. *15*:149 (July) 1955.

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THIRD ANNUAL SYMPOSIUM ON ANTIBIOTICS
Washington, D. C., November 2, 3 and 4, 1955

by
1. Shubin, H., and Heiken, C. A.
2. Morton, R. F.; LaCaille, R. A.; Gold, A., and Prigot, A.
3. Payne, H. M.; McKnight, H. V., and Harden, K. A.

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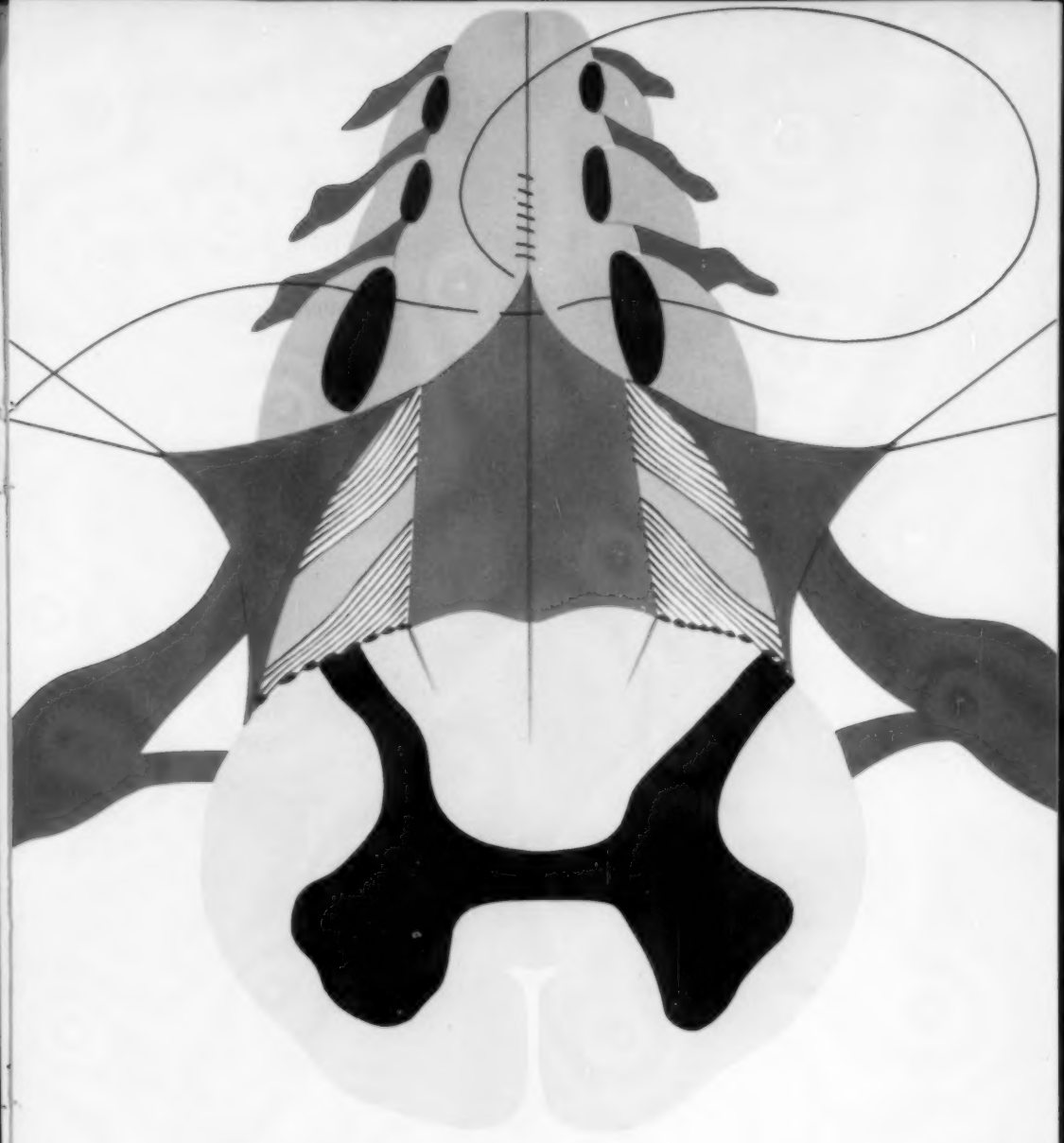

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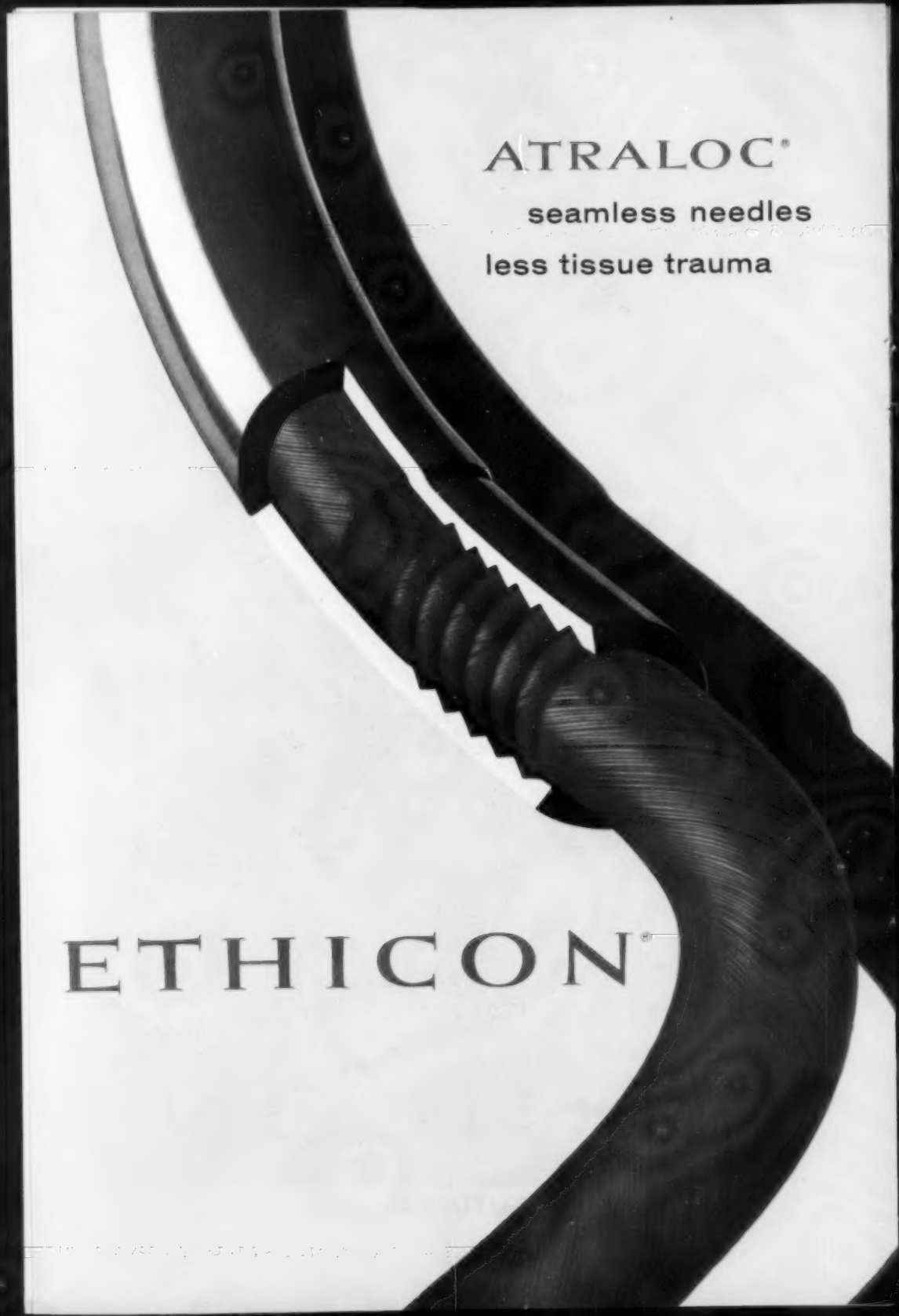
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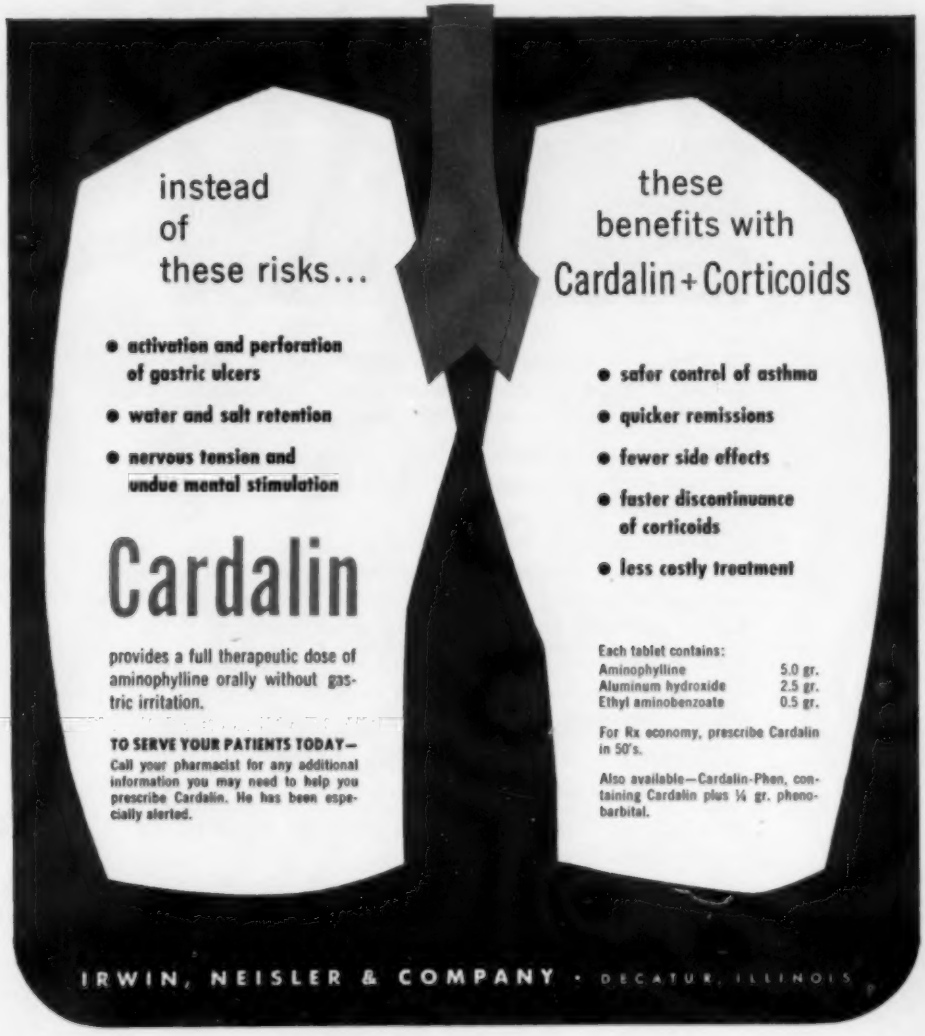
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1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.
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DISEASES of the CHEST

VOLUME XXX NOVEMBER, 1956 NUMBER 5

Heart Failure: Its Treatment— With Special Reference to Chronic Lung Disease

ARTHUR M. MASTER, M.D., F.C.C.P.

New York, New York

Heart Failure in General

Though the cardiac output may be normal or high in congestive heart failure associated with thyrotoxicosis, anemia, beriberi, Paget's disease, arteriovenous fistulae, or chronic pulmonary disease, it is, nevertheless, inadequate to supply the needs of the body tissues. A similar inadequacy exists in congestive heart failure associated with hypertensive, arteriosclerotic, or rheumatic heart disease, when the cardiac output is low or normal. In the treatment of the latter type of congestive heart failure, therefore, it is important to increase the cardiac output.

For this purpose, digitalis is effective. It increases the cardiac output in both types of congestive heart failure, but is more efficacious in cases in which the output is low. Digitalis acts directly on the heart muscle, both right and left, and increases its contractile force. The exact mechanism of the cellular change which results in improved myocardial contraction has, however, not yet been determined. It has been suggested that the primary effect of digitalis may be on the venous system, resulting in a diminution of the venous return to the heart, but no definite confirmatory evidence of this has been presented.

If the patient is acutely ill and immediate digitalization is necessary, strophanthin K or ouabain (G strophanthin) should be given *intravenously*. These drugs have a brief latent period. They usually become effective in from five to 15 minutes. Their maximum effect is attained in from 30 minutes to two hours. Lanatoside C (cedilanid) may also be given intravenously. It has a slightly longer latent period than strophanthin, and causes a decrease in the heart rate in from 20 minutes to two hours. Since its effect is more prolonged than that of strophanthin K or G, cedilanid is ideal, if moderately quick and slightly prolonged action is required. The initial dose is one 4 cc. ampule (0.8 mg.), which is approximately one-half the digitalizing dose. Thereafter, one 2 cc. ampule (0.4 mg.) is given every four to six hours, as may be required.

Because these preparations are eliminated fairly rapidly, their full digitalization effect should be maintained by the administration of a longer-acting oral digitalis preparation, as soon as practicable, i.e., within 24 hours. It is usually not necessary to use intravenous preparations for

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this purpose, except in patients with severe heart failure with rapid ventricular rate, or in an emergency, e.g., pulmonary edema.

For oral use, digoxin, a glycoside of digitalis lanata, is safe and satisfactory. It has a definite, constant composition. Unlike digitalis leaf, it is almost completely absorbed from the gastrointestinal tract, and is eliminated rapidly. It is, therefore, not as apt to cause cumulative toxic effects, such as may result from the more slowly excreted glycosides like digitoxin. The effect of a full dose of digoxin usually persists only for several days, whereas the effect of a full dose of digitoxin may continue for from two to three weeks. Digoxin may also be used intravenously, when a moderately rapid effect is required.

We have recently used *gitalin* (amorphous), a digitalis preparation which is also rapidly and completely absorbed. It has a more prolonged effect than digoxin, and a less prolonged effect than digitalis leaf or digitoxin. The major advantage of gitalin appears to be the wide margin of safety between its effective therapeutic and toxic dose. The usual therapeutic dose of most digitalis preparations is approximately two-thirds of their toxic dose; the therapeutic dose of gitalin is reported to be approximately only one-third of its toxic dose. Several patients, who developed signs of "overdosage" while on other digitalis preparations, have been able to continue digitalization with gitalin, without developing symptoms of intoxication.

The amount of any digitalis preparation required for digitalization varies greatly with each patient. The *dosage must, therefore, be individualized.* The effective dose of *digoxin* is between 1.5 and 5.0 mg. The initial dose is 1.0 to 1.5 mg.; thereafter, 0.5 mg. is given every six hours, until the desired effect is obtained. The maintenance dose is 0.25 to 0.5 mg. (one to two tablets) daily; most patients do well on 0.25 mg. Frequently, the administration of 0.25 mg. and 0.50 mg. on alternate days proves satisfactory. If *gitalin* is used, the patient may be rapidly digitalized by an initial dose of 2.5 mg., followed by 1.0 mg. every six hours. Slow digitalization may be accomplished with this preparation by giving 1.0 mg. every four to six hours, or 0.5 mg. four times daily, until digitalization occurs. The average effective dose of gitalin varies between 6.0 and 7.5 mg.; maintenance is usually achieved with 0.50 to 0.75 mg. daily.

Lanatoside C (cedilanid) is marketed in 0.5 mg. tablets. It is a crystalline glycoside, which acts rapidly and is rapidly eliminated from the body. It is administered as are the other digitalis preparations. The digitalizing dose range is between 5 to 10 mg. The maintenance dose is usually one 0.5 mg. tablet a day.

Digitoxin—Digitoxin (digitaline Nativelle, crystodigin, purodigin, etc.) is prepared in tablets of 0.05, 0.1, 0.15, and 0.2 mg. It is a pure digitalis glycoside of constant potency. Thus, biologic assay is unnecessary. It is administered, as are the other digitalis preparations, if the patient has had no digitalis for three weeks previously. The commonly used 0.1 mg. tablet is effective for 10 pounds of body weight. It has been suggested that the initial dose be 12 tablets (1.2 mg.), rather than six to eight, but this is

not advisable. The dose range for full digitalization by digitoxin is usually from 1.0 to 3.0 mg. The commonly employed daily maintenance dose is 0.1 to 0.2 mg.

Tablets of 0.2 mg. of digitoxin are not infrequently prescribed, but the simplest and safest procedure is to base the calculations of dosage on the 0.1 tablet strength. Gold reported that the daily maintenance dose of 0.2 mg., which he advised, could safely be given to only three of every four patients. Yet, this and even larger doses have been mistakenly prescribed for all patients. Digitoxin has a strong cumulative action. Overdosage produces toxic effects, which, therefore, persist for a longer period than the toxic effects of other preparations of digitalis. Hence, greater caution is necessary in its administration.

Digitoxin is the least satisfactory of the glycosides, simply because physicians administer it without sufficient caution and supervision. Fortunately, they are beginning to appreciate the dangers inherent in its use.

Many physicians still use the *whole digitalis leaf* preparation for both digitalization and maintenance. It is very efficacious, but relatively slow in its action. Its delayed effect and the long period required for its dissipation are often disadvantageous. Yet, when a patient does not cooperate and does not take the prescribed medication regularly, the use of the leaf is preferable; the effect of digoxin, e.g., disappears in about 48 hours, and the patient may go into cardiac failure, if he neglects to take it for two or three days. This is less likely when digitalis leaf is used. It should be borne in mind that the whole leaf is much safer than digitoxin.

Digitalization by the whole leaf can usually be produced by the administration of a 1½ gr. tablet (0.1 gm.) for each 10 pounds of body weight. A patient weighing 150 pounds thus usually requires 15 tablets or 22½ gr. for digitalization. Half of this amount (seven or eight tablets), is given initially, the remainder over a period of 24 to 48 hours, as desired. If the patient weighs less or more than 150 pounds, the number of tablets is diminished or increased, according to the weight. The usual maintenance dose with the whole leaf is 1 to 3 gr. daily.

Digitalization by any of the other commonly used oral preparations is attained in a similar way. Seven or eight of the daily maintenance tablets (e.g., 0.25 mg. digoxin, 0.1 mg. digitoxin, 0.5 mg. gitalin, or 0.5 mg. lanatoside C) are given initially to patients who have taken no digitalis for at least three weeks. The remaining seven or eight tablets are given over a period of one to two days, as desired, usually one every six or eight hours.

After the initial quantity of one-half the total digitalization dose has been given, each patient should be observed carefully for signs and symptoms of *digitalis intoxication*. The earliest are anorexia, asthenia, abdominal distention, cramps or pain, and visual disturbances (yellow or green vision, and scotomata). Occasionally, cerebral symptoms (confusion, dizziness, and delirium) appear. Nausea, vomiting, and diarrhea occur in most cases of digitalis overdosage, but may be late manifestations.

The most significant sign of over digitalization is arrhythmia, re-

sulting commonly from ventricular premature beats. These may occur in twos and threes, and produce bigeminal or trigeminal rhythm. Bradycardia and various degrees of A-V block may also appear. It must be emphasized that premature beats may be found in patients who are not nauseated and who do not vomit. when they do occur, the drug should be discontinued or the dosage decreased. If, despite this, the premature beats persist, they are obviously not caused by the digitalis. Depression of the RS-T segment and/or inversion of the T-wave in the electrocardiogram are evidence that digitalis has had an effect on the heart muscle, but are not, *ipso facto*, proof of intoxication.

The arrhythmias resulting from digitalis overdosage usually disappear spontaneously, if the drug is discontinued. Treatment for the arrhythmias is ordinarily not necessary. If digoxin was used, they disappear within two to three days; if digitoxin was given, the arrhythmias may persist for from two to three weeks. In some instances of supraventricular tachycardias, ventricular premature beats, or ventricular tachycardias induced by digitalis, however, specific treatment may be needed. In these cases, the oral administration of potassium chloride, acetate, or citrate usually eliminates the arrhythmias within 30 minutes. Two to 10 grams of a 20 per cent solution may be given in syrup of citric acid or Karo syrup, or smaller quantities may be given in milk, orange juice, or ginger ale. Administration of 5 to 10 cc. of Potassium Triplex (Eli Lilly) in orange juice (5 cc. contains 0.5 gm. each of potassium acetate, potassium citrate and potassium carbonate) is also efficacious, but its effect lasts only for from two to four hours. The treatment may, therefore, have to be repeated. Toxic effects due to the potassium do not occur, if there is adequate urinary excretion. Rarely is it necessary to administer potassium intravenously; if it is, extreme caution should be used, and only 0.5 to 1.5 gm. should be given slowly. Electrocardiograms should be taken frequently, to detect potassium intoxication. Its most common effect is marked peaking of the T-waves, widening of the QRS complexes, and disappearance of the P-waves.

That *potassium depletion* may sensitize the myocardium to the toxic effects of digitalis has recently been proved. Conversely, the presence of adequate cellular potassium may actually prevent toxic digitalis effects. For these reasons, potassium should usually be given to patients who require large doses of digitalis. Arrhythmias may thereby be prevented.

Orange juice has a relatively high potassium content and may be efficacious in combating digitalis intoxication. Atropine, too, may be given by mouth or parenterally. Quinidine has been advocated. As a result of experiments on dogs, aminophylline and theobromine sodium acetate have also been recommended to reduce the toxic effect of digitalis. For the most serious manifestation of digitalis intoxication, i.e., ventricular tachycardia, pronestyl should be administered intravenously. Whenever possible, intravenous pronestyl should be given under direct electrocardiographic control. The drug should be administered at no more rapid a rate than 100 mg. per minute up to a maximum of 1 gram. One should be alert

for evidence of over-effect, that is widening of the QRS complex on the electrocardiogram and hypotension. The drugs now commonly employed for the prevention of alleviation of motion sickness have been successful also in combating the nausea produced by digitalis.

It is often extremely difficult to distinguish arrhythmias or symptoms due to *"overdigitalization"* from those due to inadequately treated heart failure or *"underdigitalization."* It may occasionally be impossible to decide whether to withdraw digitalis or to administer larger doses to patients who receive digitalis, and yet remain in severe heart failure, have a rapid ventricular rate, and suffer from nausea and vomiting. To determine whether or not a patient is adequately digitalized, a test has been developed, which utilizes a rapidly acting digitalis preparation, acetyl-strophanthidin. Since the effect of this preparation appears within one to 10 minutes after its intravenous administration, the status of the patient may be quickly determined; if the patient is adequately "digitalized" or "overdigitalized", toxic effects usually appear after the injection of less than 0.6 mg. of acetyl strophanthidin. If these effects do not appear, overdigitalization is usually not the cause of the symptoms or the arrhythmia. Acetyl-strophanthidin, however, is extremely potent, and several fatalities have resulted from its use. We, therefore, prefer to use as test drugs either intravenous lanatoside C (cedilanid), 0.4 mg. every three hours, or strophanthin K, 0.1 mg. every 30 to 45 minutes. One to three doses are given. Though the results obtained thereby are slower (four-six hours), this method is safer, and adequately differentiates between over and underdigitalization.

In elderly and aged patients, the required effective dose of digitalis is usually considerably smaller than in the young, because there is a great increase in sensitivity to digitalis in old age. This must be borne in mind, since the number of elderly patients with heart failure is steadily increasing with the increase in the number of older people.

Adequate *salt restriction* and use of *mercurial diuretics*, to aid sodium excretion, are also of prime importance in the management of congestive heart failure. The importance of *adequate rest*, either in a chair or in bed, especially during the initial period of treatment, cannot be emphasized too strongly.

Phlebotomy is of great value in acute left heart failure secondary to arteriosclerotic heart disease, i.e., cardiac failure with a low output; if, however, phlebotomy is performed in heart failure associated with chronic anemia, arteriovenous fistulae, or pulmonary disease, e.g., it may be very harmful, for a high output is necessary to maintain adequate tissue oxygenation in these conditions, and measures that lower the blood volume, such as phlebotomy, further decrease the amount of oxygen available to the tissues. *Hexamethonium*, a ganglionic blocking agent (10 to 50 mg. intravenously), has been advocated in the treatment of acute congestive failure. Through vasodilation and peripheral pooling of blood, it reduces the venous return and relieves the overdistended myocardium, without actually withdrawing blood. Though the use of hexamethonium is physi-

ologically sound, its administration must be carefully supervised. It should not be used routinely in the treatment of a condition that can usually be controlled in other ways. It may be indicated, however, in patients with failure associated with severe hypertension.

In cases of severe heart failure, during the first few days, when the degree of pulmonary congestion is considerable, *penicillin* (300,000 to 600,000 units daily in a single dose) or other antibiotics should be administered, in order to prevent secondary lung infection.

Attacks of *paroxysmal nocturnal dyspnea* are often completely overcome by having the patient sit up, stand, or walk about, if possible. Mild cases can often be controlled by aminophylline suppositories (0.5 gm.-7½ gr.), but it may be necessary to give the aminophylline intravenously (0.5 gm.), very slowly, and preferably in dilution. In more severe cases, which do not respond to aminophylline, *morphine sulfate* should be given intramuscularly (15 mg.-¼ gr.) or intravenously (8 to 10 mg.-⅛ to ⅙ gr.). The intramuscular route is usually satisfactory. Morphine usually effectively suppresses the pulmonary reflexes that serve to perpetuate symptoms. If the attack persists, treatment for pulmonary edema should be instituted. In chronic cor pulmonale, morphine is dangerous, because it depresses the respiratory center.

Attacks of *cardiac asthma* can usually be prevented by the measures employed in the treatment of congestive failure, i.e., a low sodium diet, digitalization, and mercurial diuretics. In some of the milder cases, digitalization may not be required. Sleeping on several pillows or, in severe cases, in a chair may prevent the appearance of symptoms.

Acute Pulmonary Edema: The onset of acute pulmonary edema, secondary to left ventricular failure, may be extremely sudden, with signs of circulatory collapse, severe dyspnea, and cyanosis. *Morphine sulfate* (15 mg.-¼ gr.) should be given intramuscularly at once. In cases with peripheral collapse, in which little or no absorption can occur, intravenous administration (8 to 10 mg.-⅛ to ⅙ gr.) is necessary. Morphine usually produces dramatic improvement; if it does not, the injection should be repeated in 15 to 20 minutes. Dilaudid (2 to 3 mg.-1/32 to 1/20 gr.), Pantopon (20 to 30 mg.-⅓ to ½ gr.), or Demerol (100 mg.) may be used instead of morphine, especially if the latter induces vomiting. Although some physicians use atropine (0.4 to 0.6 mg.-1/150 to 1/100 gr.), routinely in the treatment of acute pulmonary edema, it is of little value. And when tachycardia is present, atropine may actually be harmful.

Despite the fact that the arterial blood is fully oxygenated in many cases of heart failure, *oxygen* is of value in pulmonary edema. Often, when given by the meter mask, under pressure (3 to 6 cm. of water), its effect is dramatic. After the initial attack has been controlled thereby, recurrence of pulmonary edema may occasionally be prevented by the administration of oxygen for 15 minutes every few hours, until 10 to 12 hours have elapsed. It should be remembered that the percentage of oxygen inspired by a patient, when a nasal catheter or tent is used (35 to 65 per cent) is not as great as that inspired through a mask (50 to 100

per cent). Pressure breathing is most efficacious in all left ventricular failure, not only in pulmonary edema but also in cardiac asthma, and in nocturnal and paroxysmal dyspnea. By retarding the entrance of blood into the right heart, the right and left ventricles are offered an opportunity to work with a smaller load.

Intravenous aminophylline (0.5-7½ gr.) is of particular value in the treatment of acute pulmonary edema, when Cheyne-Stokes respiration is present. The intravenous injection should be given very slowly; it should consume at least six minutes and preferably 12 minutes. It is more desirable, however, to administer the aminophylline by the drip method, in 100 cc. of 5 per cent glucose solution. Barach found that the rectal administration of aminophylline (0.6 gm. dissolved in 20 or 30 cc. of tap water) was efficacious. Aminophylline is particularly useful in pulmonary conditions, e.g., bronchial asthma, since it relieves bronchospasm.

If pulmonary edema persists despite this treatment, 0.3 mg. of *strophanthin K* or 0.5 mg. *ouabain* (strophanthin G) should be given intravenously. Cedilanid (lanatoside C) or digoxin may also be used intravenously (the digoxin preparation now available may be used without further dilution).

Two cc. of a mercurial diuretic should also be administered. Though it may be more toxic when given intravenously, it should be administered intravenously in acute emergencies, i.e., when a patient is in shock, and when absorption otherwise is poor. Intramuscular or subcutaneous injections of the mercurial diuretics should be given thereafter, since these are almost as efficacious as the intravenous injections.

Bloodless phlebotomy by means of *tourniquets*, if employed properly, may be effective in patients with pulmonary edema secondary to low output cardiac failure. If definite improvement does not occur after 45 or 60 minutes, phlebotomy should be performed, 500 to 800 cc. of blood being withdrawn rapidly. If the hemoglobin and hematocrit are definitely reduced, however, phlebotomy should not be considered.

The use of *antifoaming agents* in the treatment of acute pulmonary edema has not become widespread, despite the enthusiastic reports of some observers. *Alcohol vapor by inhalation* is said to penetrate the finer air spaces and to alter the surface tension at the fluid-air interspace, thereby collapsing the foam bubbles and bringing relief, when all other measures have failed.

Maintenance Therapy of Congestive Heart Failure: After the acute attack of failure has been overcome, the usual management of congestive heart failure should be instituted. Digitalis maintenance with a suitable preparation (digoxin, 0.25 to 0.50 mg. or gitalin, 0.50 to 0.75 mg. per day), a low sodium diet, and the judicious use of mercurial diuretics are the three cardinal measures employed in long-term therapy.

Adequate restriction of salt can now be achieved, while the patient enjoys a *reasonably well balanced, palatable diet.* During the first week after the acute episode of heart failure, a diet containing less than 1 gm.

of sodium should be prescribed. Such a diet includes fresh fruits, unsalted vegetables, potatoes or rice, cottage cheese, salt-free bread, and salt-free milk prepared from "lanolac" powder. The "lanolac" may be made more palatable by the use of vanilla flavoring. It provides a high protein intake with minimal sodium, whereas whole milk has approximately 500 mg. of sodium in 1000 cc. The *Walker-Gordon Company* has just placed a palatable *low sodium milk* on the market. If the patient does well on this regimen, small portions of meat and fresh-water fish may be given.

It is important that the patient *chart* his *weight daily*, preferably graphically. Thus, the retention of even small amounts of fluid can be more readily detected. Five to eight pounds of edema fluid may accumulate, before clinical signs (rales or ankle edema) appear.

In severe congestive failure, the *mercurial diuretics* have displaced digitalis as the backbone of therapy. Since exercise increases sodium retention, patients are instructed to remain in bed for an hour or two following each mercurial injection, during the early stages of treatment. The maximum diuretic effect may thus be obtained. Oral mercurial diuretics may also be efficacious. Careful attention, however, must be paid to the electrolyte balance in older persons, who receive mercurials. Occasionally, ammonium chloride (4 to 6 gm., 60-90 gr., a day for two to three days), given before the mercurial, may increase its effectiveness. Aminophylline, 0.5 gm. (7½ gr.) given intravenously, increases the renal blood flow and, when administered one to two hours after a mercurial diuretic, may also markedly increase the diuretic response. Mercurials may be given to patients with renal disease, unless there is oliguria or azotemia.

While the daily injection of a mercurial diuretic is usually safe in the young, it may be dangerous in the *elderly*. After the acute attack of heart failure has subsided, these patients should be given 1 cc. of Mercuhydrin or Thiomerin, at most every other day. In elderly men, mercurials often aggravate the symptoms of prostatic disease, causing acute retention and uremia. The use of an indwelling catheter often prevents this, and permits the continuation of the diuretic therapy. It has been shown that morphine, Demerol, quinidine, barbiturates, ephedrine, and adrenalin often decrease the effectiveness of the mercurial diuretics. This should be borne in mind, if any of these drugs must be given simultaneously with the mercurials.

Diamox, a carbonic anhydrase inhibitor that increases the excretion of sodium, potassium, and bicarbonate, is a relatively new oral diuretic agent, and may be useful in the management of some cases of cardiac

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Footnote: The judicious use of the mercurial diuretics, adequate salt restriction, and digitalization, with sufficient fluid intake for adequate kidney function, usually control cardiac failure. In some patients with refractory edema, however, and in others who cannot maintain a salt-poor diet, the use of *cation exchange resins* may be justified, if given under close supervision. The resins are substances capable of "binding" ingested sodium within the intestinal tract, and excreting it in the stools. The ammonium cation exchange resins, with added potassium, are the most satisfactory. The danger of inducing acute hypokalemia, through the loss of excessive potassium in the stools, is minimized when they are used.

failure. Profuse diuresis and resultant clinical improvement have occasionally resulted from its use. Since Diamox, in a still undefined way, decreases CO_2, it is useful, at least theoretically, in preventing CO_2 narcosis in heart failure associated with chronic cor pulmonale. However, if a patient already has respiratory acidosis, it is not safe to give Diamox. It is questionable if it is of any aid in lowering the Co_2 in ambulatory patients. The increased CO_2 in pulmonary emphysema has some advantages, unless the patient is shifted to the acid side in which case stupor or coma may occur.

When fluid accumulates rapidly in the chest, and causes acute distress, immediate and repeated *thoracenteses* occasionally give remarkable relief and permit recovery. Though some fluid may accumulate in the abdominal cavity also, it rarely causes symptoms or requires paracentesis. However, in rare cases, this, too, has proved successful. Southey tubes may aid in draining fluid from the lower limbs.

Dicumarol may be given to prevent the occurrence of phlebothrombosis and embolism, particularly in patients who are expected to be bedridden for a long period of time. The efficacy of this measure has been questioned by some observers. In our experience, however, anticoagulant therapy has proved to be of value.

The use of Dramamine, Thorazine, and other anti-motion sickness drugs, has greatly facilitated the treatment of the *nausea and vomiting* that complicate congestive heart failure.

Treatment of intractable *hiccup* is extremely difficult. Repeated reassurance is essential. Many drugs and maneuvers have beeen advocated, each of which is occasionally successful. Sedation, amyl nitrite, intravenous niacin, inhalation of 5 to 7 per cent CO_2 and 90 per cent oxygen for a few minutes at a time, inhalation of ether, ethyl chloride spray to the region over the diaphragm, and intramuscular injections of quinidine (0.4 gm.-6 gr.) three times a day should all be tried in turn, in the hope that one will be efficacious. Thorazine in large doses (25 mg. every four hours) is sometimes helpful, perhaps because of its sedative effect. Phrenicectomy or exeresis is occasionally required to overcome a severe attack.

Acute Cardio-Pulmonary Insufficiency: The treatment of acute right heart failure associated with chronic pulmonary disease is difficult. It differs, in many respects, from the general treatment of acute left ventricular failure, or congestive heart failure. The right heart failure associated with acute pulmonary infection in patients with chronic bronchitis, bronchial asthma and pulmonary emphysema is usually reversible, and more amenable to treatment, than is the failure associated with severe pulmonary fibrosis (e.g., pneumoconioses). There is a host of interstitial pneumonias also (Hamman-Rich disease, pneumonias of viral, spirochaetal, fungal, protozoan, and parasitic origin) which increases the work of the right heart. If this persists, right heart hypertrophy (cor pulmonale) results. Conversely, chronic congestive heart failure in mitral stenosis, may be associated with permanent changes in the lungs. In idiopathic

pulmonary artery dilatation, the pulmonary structure becomes irreparably damaged.

It is important to differentiate between chronic pulmonary insufficiency and heart failure. In chronic lung disease, dyspnea is an early pulmonary symptom, and appears before heart failure occurs. Study of the circulation time and determination of the venous pressure are helpful in the differential diagnosis. In pure pulmonary disease, these are not increased. It may be difficult to distinguish the cyanosis due to congenital heart disease, in which unaerated blood is shunted to the arterial system, from the cyanosis due to chronic lung disease, in which the blood from the right heart is poorly aerated in the lungs. The arterial blood carbon dioxide is below normal in the former, but normal or raised in the latter. It is almost invariably raised in patients with congestive heart failure complicating bronchitis or emphysema.

In acute right heart failure, severe anoxia is usually present, since the degree of oxygen exchange in the lung alveoli is markedly diminished. Delirium, stupor and coma may appear. Cough productive of much thick sputum compromises the airway.

The ventilatory anoxia increases the tone of the pulmonary vessels, by direct action on them and, thereby, increases the pulmonary artery pressure. This effect is more marked in patients in whom there is a reduction of the pulmonary vascular bed. Chronic anoxia may also produce hypervolemia, increased cardiac output, and polycythemia. The increased blood volume and cardiac output further increase the volume of blood in the pulmonary circulation, and further limit the capacity of the pulmonary vascular bed. The polycythemia, with its increased blood viscosity, increases the resistance to blood flow and helps raise the pressure in the pulmonary artery. These various mechanisms combine to produce pulmonary hypertension. When the hypertrophied right ventricle, whose function is also impaired by the direct action of the anoxia on the myocardium, is no longer able to cope with the increased pulmonary resistance and the demand for increased cardiac output, right ventricular dilatation and cardiac failure result.

Acute right ventricular failure may sometimes develop as a result of *physical overactivity, infection,* or *emotional upset.* The occurrence of pneumonia and bronchial obstruction in patients with reduced pulmonary vascular bed, causes further reduction of the vascular bed, and produces still greater resistance in the pulmonary circuit. This is proved by the low vital capacity and reduced maximum breathing capacity found in these cases. The fever, induced by the pulmonary infection, causes a rise in oxygen consumption, due to increased metabolic requirements. The rise in oxygen consumption is generally accompanied by an increased cardiac output, which, in turn, may lead to an increased pulmonary blood flow and further embarrassment of the pulmonary circulation.

The respiratory center is indirectly stimulated by the anoxia acting on the carotid sinus chemoreceptors. If *oxygen* is administered in high concentration (100 per cent), suppression of respiration may occur, and

CO_2 may accumulate (respiratory acidosis). The administration of oxygen in high concentration may, therefore, be dangerous, and even cause coma and death.

Oxygen in high concentration may be given, if adequate respiration is maintained simultaneously by the use of mechanical respirators. Hospitalization of the patient and careful supervision are, however, necessary. Automatic machines can deliver oxygen under slightly *increased expiratory pressure*. This may prevent pulmonary edema and left heart failure. It may also dilate the alveoli and make expiration easier, thus aiding in the elimination of CO_2. The use of the respirator for from 10 to 20 hours a day may be necessary for from 10 to 14 days. Oxygen, under ordinary atmospheric pressure, may be administered by a simple, lightweight, transparent plastic face mask with an open upper end. The oxygen enters at the bottom of the mask, passes over the oranasal area, and carries the carbon dioxide out through the upper end. The mask is inexpensive and can be sterilized. It is comfortable. It may be lifted from the chin, if the patient desires to expectorate. It delivers 30 to 55 per cent concentration of oxygen, with a flow of 4 to 6 liters per minute. The double-bent nasal tube is still a comfortable and simple way of furnishing oxygen.

Bronchial infection is a prime trigger mechanism, which may precipitate heart failure. Antibiotics, therefore, should be given daily to combat possible *infection*, in all cases of congestive failure, whether or not there is associated pulmonary disease. In addition to systemic antibiotic therapy, the drugs may be administered in the nebulized sprays or aerosols which the patient breathes with his oxygen.

The use of *nebulized bronchodilators* immediately and at frequent intervals is most beneficial. Epinephrine derivatives, such as isoproteranol, are best. They are commonly employed vaporized, and are efficacious in a 1:100 dilution (e.g., Isuprel, 5-10 drops in a nebulizer, inhaled for from 10 to 15 minutes every four hours). Sublingual administration of these drugs sometimes relieves the bronchospasm. Antihistamines are only occasionally helpful. Intravenous aminophylline, given slowly, preferably in dilution, is particularly useful.

The elimination of bronchial secretions is essential. Barach's exsufflator, to aid cough, may be helpful. In resistant cases, tracheobronchial suction or even tracheotomy may be required. The age-old remedy, of saturated solution of potassium iodide, 10 drops, t.i.d., is often of value in the liquefaction of tenacious inspissated bronchial secretions.

Several moderately priced electromechanical machines have been devised, which deliver bronchodilator aerosols, antibiotics, cold water vapors for increasing the humidity of the air or oxygen breathed, anticholinergic agents in certain types of bronchoconstriction, pus liquefying enzymes, detergent agents, and dusts or emulsions of cortisone and hydrocortone. There are exsufflators, which alternate positive-negative pressures and produce coughing, thus aiding in the elimination of bronchopulmonary secretions. Other devices produce intermittent positive pressure during

inspiration only. Suction outlets are provided whenever mild aspiration is needed, e.g., in accumulation of secretions in the trachea.

Digitalis, mercurial diuretics, and a low sodium diet are of great value in right heart failure caused by chronic pulmonary disease, as they are in the left ventricular failure due to heart disease. In cor pulmonale, the heart rate may be rapid, due to hypoxia; it cannot, therefore, be used as a reliable indicator of the digitalis effect in this condition.

Cortisone and Corticotropin have been helpful in chronic asthma and particularly in status asthmaticus. Prednisone drugs now promise to be more successful, even in smaller dosage. There is less retention of sodium and water, and no excessive potassium depletion.

Morphine, codeine, and the barbiturates are undesirable, since they depress respiration, but *chloral hydrate* or *paraldehyde* may be given, if necessary. Morphine is particularly hazardous, and sometimes causes death. It has been suggested that Dilaudid does not cause the bronchial constriction which morphine does produce. Nalline is said to be useful in combating the danger of respiratory acidosis resulting in depression of the respiratory center by opiates. As a sedative, Demerol in doses of no more than 40 mg. intramuscularly does not depress respiration and often is of aid in pulmonary emphysema.

Recently, *phlebotomy* has been advocated to reduce blood volume. It is occasionally lifesaving. The secondary polycythemia is considered to be disadvantageous, and not a compensatory mechanism, when the lesser circulation fails. If the slow withdrawal of 500 cc. of blood relieves dyspnea and cyanosis, phlebotomy may be repeated every few days until 1500 to 2000 cc. of blood have been removed. (The hematocrit should be kept at between 45 to 50 per cent, and the hemoglobin at 12.0 to 12.5 gm.). The heart muscle in cor pulmonale, unlike that in rheumatic and arteriosclerotic heart disease, is usually good, and may react well to a decrease in circulating blood volume. When the blood volume is not increased, cell transfusions are sometimes necessary to overcome an associated anemia.

Sudden death is not uncommon in cor pulmonale. It occurs in the last stages of the disease, with severe congestive failure.

Acute cor pulmonale may be caused also by *pulmonary infarction* or *overwhelming pulmonary infection*, in the absence of chronic disease of the lungs. The possibility of its occurrence should, therefore, always be borne in mind.

Arrhythmias are much less common in cor pulmonale than in other cardiac diseases. Hydrothorax is rare, and usually indicates a complication, such as pulmonary infarction. Loss of weight in obese patients with chronic lung disease is particularly desirable; in uncomplicated extreme obesity, a syndrome of somnolence, Cheyne-Stokes respiration, intermittent cyanosis, and polycythemia, with congestive heart failure, has been described.

SUMMARY

In heart failure associated with chronic cor pulmonale, the best results are obtained from (1) the use of antibiotics, to overcome pulmonary in-

fection; (2) the liberal use of nebulized bronchodilators, to help relieve bronchiolar obstruction by expulsion of bronchial secretions; (3) digitalization to improve the function of the right ventricle; (4) sodium restriction; (5) the administration of mercurial diuretics; and (6) the judicious reduction of the hypervolemia by phlebotomy. Diamox is especially worth a trial. Oxygen therapy is beneficial also, but it should be used cautiously and intermittently, lest carbon dioxide narcosis develops. Artificial respiration may be lifesaving.

RESUMEN

En la insuficiencia cardiaca asociada al corazón pulmonar crónica, se obtuvieron los mejores resultados de: (1) el uso de antibióticos para dominar la infección pulmonar; (2) la aplicación liberal de broncodilatadores por nebulización para ayudar a mejorar la obstrucción bronquiolar y favorecer la expulsión de las secreciones; (3) la digitalización para mejorar la función del ventrículo derecho; (4) la restricción de sodio; (5) la administración de diuréticos mercuriales y (6) la juiciosa reducción de la hipervolemia por la flebotomía. El Diamox es especialmente digno de emplearse. La oxigenoterapia es benéfica también, pero debe usarse con cautela e intermitentemente pues puede presentarse la narcosis por el dióxido de carbono. La respiración artificial puede salvar vidas.

RESUME

Dans la défaillance cardiaque du coeur pulmonaire chronique, les meilleurs résultats sont obtenus: (1) par l'utilisation des antibiotiques, pour juguler l'infection pulmonaire; (2) par l'utilisation sans restriction d'aérosols bronchodilatateurs, pour empêcher l'obstruction bronchiolaire en expulsant les sécrétions bronchiques; (3) par le traitement digitalinique pour améliorer la fonction du ventricule droit; (4) par le régime désodé; (5) par l'administration de diurétiques mercuriels; (6) et par la réduction judicieuse du volume sanguin par la phlébotomie.

Le Diamox vaut la peine d'être essayé. L'oxygénothérapie est aussi salutaire, mais elle doit être utilisée avec prudence, et par intermittence, à moins que ne se développe une somnolence due au bioxyde de carbone. Grâce à la respiration artificielle, on peut arriver à sauver la vie.

ZUSAMMENFASSUNG

Bei Herzschwäche in Verbindung mit chronischem cor pulmonale ergeben sich die besten Resultate (1) durch den Gebrauch von Antibioticis, um pulmonale Infektionen zu überwinden; (2) durch den reichlichen Gebrauch von zerstäubten Bronchodilatatoren, um dazu beizutragen, den bronchiolären Verschluss zu beheben mittels Entleerung des Bronchial-Sekretes; (3) durch Digitalisierung zwecks Verbesserung der Leistung des rechten Tentrikels; (4) Na-Einschränkung; (5) durch die Anwendung von Quecksilber-Diureticis; (6) durch die geschickte Reduzierung des erhöhten Blutvolumens durch venae sectio.

Im besonderen ist Diamox einen Versuch wert. Auch die Sauerstoff-Therapie ist von Nutzen, aber man muss sie behutsam und intermittierend anwenden, damit keine CO_2-Narkose auftritt. Künstliche Atmung kann lebensrettend sein.

The Effects of Corticotropin (ACTH) and Cortisone in Fifteen Cases of Pulmonary Tuberculosis*

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Despite numerous studies reported during the past six years, the controversy concerning the effects of ACTH and cortisone on tuberculous infections continues. When one considers the many known and unknown factors that influence host-parasite relationships, the different reactions of different species to tuberculous infections, and the varied effects of different drugs and hormones on the infecting organism, the persisting controversy is not surprising.

Administration or exogenous ACTH stimulates increased production of not only catabolic glucocorticoids, such as hydrocortisone and cortisone, but also anabolic androgenic and estrogenic "N" hormones and mineral corticoids.

In contrast to ACTH, the administration of exogenous cortisone or hydrocortisone may increase the blood level of the hormone given but otherwise reduces the endogenous production of the anabolic "N" hormones and mineral corticoids as well as adrenal glucocorticoids. Hydrocortisone or cortisone therapy will also suppress the pituitary gland and its production of ACTH, TSH, gonadotropin, etc. and thereby secondarily reduce the production of adrenocortical, thyroid, sex, and other hormones.

ACTH therapy stimulates hypertrophy of the adrenal cortex and increased endogenous production of many adrenocortical hormones, whereas cortisone or hydrocortisone therapy results in atrophy of the adrenal cortex (diminished ACTH stimulation) and reduced endogenous production of adrenocortical hormones.

Thus cortisone therapy more grossly alters the over-all normal hormonal balance and interferes with more factors affecting host-resistance to stress or infection, than does ACTH therapy, because of deficencies of endogenous production of many more hormones. Theoretically, at least, these differences would suggest that ACTH might be less harmful than cortisone in infections.

Fifteen cases of active pulmonary tuberculosis were selected for complete metabolic studies of ACTH and cortisone, and the influence of these hormones upon toxic manifestations. However, because of the continuing uncertainty, confusion, and disagreement among equally reliable investigators who have used hormonal therapy in tuberculosis, a report of

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coincidental clinical, roentgenologic, and selected laboratory observations noted in this study seems worthwhile.

Case Material (Background Factors)

All patients were male veterans with proved active pulmonary tuberculosis. Seven were less than 40 years of age, and eight ranged from 44 to 57 years. Eight were white, six negro, and one was Indian. The disease was far advanced in 14 cases and moderately advanced in one (3). Cavities were present in 13 of the 15 cases and were 2.0 to 10.0 cm. in diameter in 12 (Table I). The known duration of disease was six months or less in nine cases, and from one to more than four years in four.

Eight had received chemotherapy for periods of three to 10 months. Bacilli from six of the eight cases were completely resistant to 10 mcg. of streptomycin per ml. and partially resistant in two. Two had received chemotherapy for one month and two and one-half months respectively, and partial bacillary resistance was noted in each case. Tests of bacillary

TABLE I

BACKGROUND FACTORS BEFORE HORMONAL THERAPY

Case No.	Age	Race	Stage of Dis.	Cavity (Cm.)	Dur. of Dis. (Mos.)	Drugs[1]	Dur. (Mos.)	Bact. Resist. To SM	X-ray Changes Pre-Rx
1.	29	N	F. A.	2.5	3	DHSM	1	....	Station.
2.	22	N	F. A.	0.0	2	None	0	....	Station.
3.	45	W	M. A.	0.0	1	None	0	....	Unknown
4.	28	N	F. A.	2.5	15	SM	3	CR[2]	Station.
5.	39	W	F. A.	2.0	6	SM + PAS	4	CR	Progress.
6.	55	N	F. A.	7.0	6	SM + PAS	5	PR[2]	Retrogr.
7.	52	W	F. A.	3.0	6	DHSM + PAS	2½	PR	Progress.
8.	57	W	F. A.	6.5	4.5	SM + PAS	1	PR	Progress.
9.	30	W	F. A.	4.5	21	(SM alone (PAS alone	3 7	CR	Retrogr.
10.	54	Ind.	F. A.	9.5	5+	None	0	....	Unknown
11.	44	N	F. A.	0.5	7	SM + PAS	4	CR	Progr. then Retrogr.
12.	23	N	F. A.	7.0	1.5	SM	½	....	Station.
13.	57	W	F. A.	10.0	10	DHSM + PAS	3½	PR	Progress.
14.	34	W	F. A.	10.0	52	SM + PAS	7	CR	Progress.
15.	50	W	F. A.	9.0	21	(DHSM alone (PAS alone (SM + PAS	3 3 ½	CR	Progress.

(1) The dosage of streptomycin (SM) and dihydrostreptomycin (DHSM) was one gram daily in all patients except three (Nos. 5, 6 and 8) who received one gram twice weekly. The dosage of PAS was 12.0 gms. daily.

(2) Completely resistant (CR) and partially resistant (PR) to 10 mcg. of SM per ml.

susceptibility to streptomycin were lacking in five cases. Of the latter five cases, two had received chemotherapy for 14 days and 28 days respectively and three had received no chemotherapy prior to hormonal therapy (Table I). (Only one (3) of the latter three cases received chemotherapy concurrently with hormonal therapy).

Serial roentgenograms, before hormonal therapy (Table I) revealed progression of disease in six cases, progression then retrogression in one

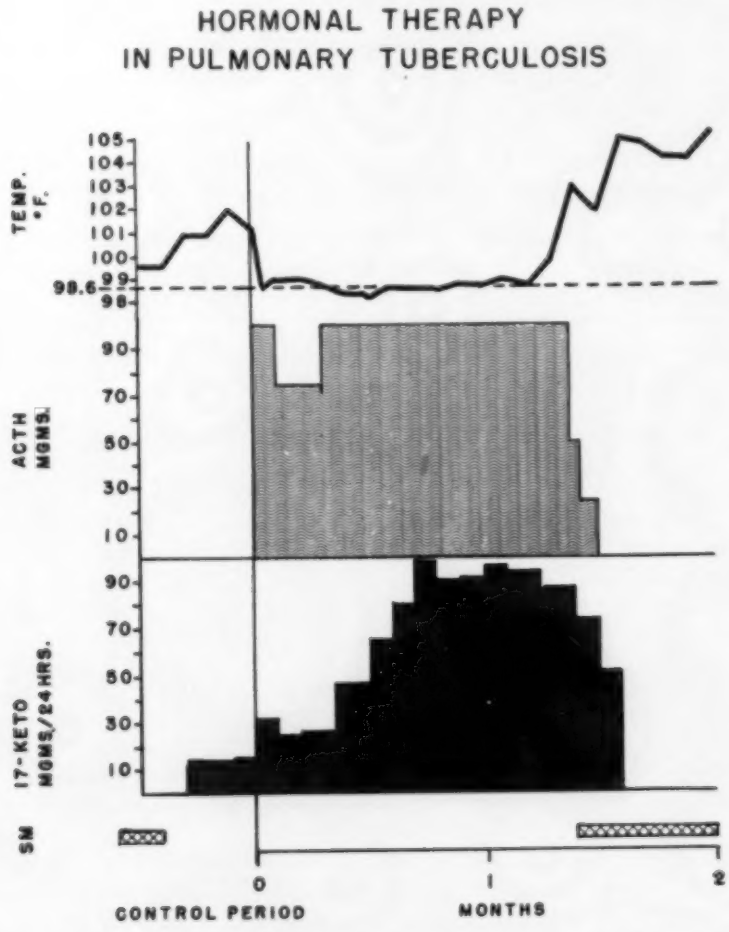

FIGURE 1: Case 1 (C. B.). This case illustrates the typical sharp defervescence of fever (representative of clinical response) in patients who received ACTH therapy. Twenty-four hour urinary excretion of 17-ketosteroids indicates ACTH effect. Note lack of concurrent chemotherapy. Dosage of hormone maintained at unnecessarily high level too long and stopped too abruptly. Sharp return of high fever and toxic symptoms upon discontinuation of ACTH therapy suggests "rebound phenomenon." (Also see Fig. 2).

(11), no change in three, retrogression in two, and the roentgenographic course of the disease was unknown in the two cases started on hormonal therapy shortly after admission.

Regimen of Therapy

The details of drugs, dosages,[1] and duration of chemotherapy given in each case before, during and after hormonal therapy, appear in Tables I, II and III respectively. The type of hormonal therapy given in each case appears in Table II. In general the earlier cases were started at a dosage of 100 or 80 mgs. of ACTH, and later cases often at 40 mgs. daily. The dosage of cortisone was 200 mgs. daily for the first two or three days, 100 mgs. daily for the next several days, and then substantially reduced. Usually the dosages of both hormones were substantially reduced following a short initial period of high dosages. The total duration of hormonal therapy was from 31 to 351 days (Table II). Soon after these studies were started (1949) we learned to stop hormonal therapy gradually.

TABLE II

ROENTGENOGRAPHIC CHANGES OBSERVED DURING ACTH AND CORTISONE THERAPY WITH OR WITHOUT CONCURRENT CHEMOTHERAPY

Case Number	Hormonal Therapy: Hormone	Dosage (mg. daily)	Dosage Total	Duration Days	Concurrent Chemotherapy	X-ray Changes
1.	ACTH	100-25	4200	45	None	Mod. worse
2.	ACTH	100-75	4175	46	None	Sl. worse
3.	ACTH	100-20	2315	62	DHSM	Sl. improv.
4.	ACTH	75-20	3840	109	SM	Mark. worse
5.	ACTH	40	3240	81	SM + PAS	Mark. worse
6.	ACTH	40-20	1080	31	SM + PAS	Sl. worse
7.	ACTH	40-20	2040	81	DHSM + PAS	Sl. improv.
8.	ACTH	40-10	6995	159	SM + PAS[2]	Sl. worse
9.	ACTH	40-10	4030	109	PAS[3]	Sl. worse
10.	Cortisone	200-20	5530	51	None	Mark. worse
11.	Cortisone	200-25	3575	38	SM	Sl. worse
12.	Cortisone	200-15	1865	31	SM	No change
13.	ACTH	75-20	5385	205	DHSM	Sl. worse
14.	ACTH Cortisone	40-20 100-20	4640 11545	116 235	SM + PAS SM + PAS	Mark. worse
15.	ACTH Cortisone	40-30 100-50	2680 4525	70 56	SM + PAS SM + PAS	Mod. worse

(1) See footnote (1) of Table I.
(2) SM + PAS given during 3 of the 5 Mos. of ACTH therapy.
(3) PAS alone given during 2 of the 3⅓ Mos. of ACTH therapy.

Table II indicates whether or not chemotherapy was given concurrently with hormonal therapy. The dosage of streptomycin or dihydrostreptomycin was one gram daily, except for three patients (5, 6 and 8) who received one gram twice weekly; and the dosage remained the same whether given before, during or after hormonal therapy. The dosage of PAS was 12.0 gms. daily (or 16.0 gms. of NaPAS) in all cases. When excessive retention of sodium and water and excess loss of potassium became a clinical problem, we found K-PAS a useful substitute for NaPAS.

Response to Hormonal Therapy

Clinical Response: In most cases, hormonal therapy resulted in dramatic clinical improvement which contrasted sharply with roentgenographic evidence of deterioration in many. The typical response was abrupt defervescence of fever and toxemia (Fig. 1), marked increase of appetite, substantial gain in weight, and improved sense of well-being.[19, 20] Although fluid retention accounted for some of the weight gain, much of it was due to marked improvement of appetite and nutrition.

Roentgenographic Response: *During hormonal therapy* (Table II) serial roentgenograms revealed evidence of progressing disease in 12 cases (80 per cent), no change in one, and slight improvement in two (3 and 7). Of the 15 tuberculous patients, three died while on hormonal therapy; and in the remaining 12, subsequent roentgenographic changes revealed marked progression in seven (58.3 per cent), no change in one, slight improvement in one, and moderate to marked improvement in three (Table III). Progression of pulmonary disease was often marked and consisted of a strong tendency to extensive cavitation and spread to new areas of the lung (Figures 2 and 3).

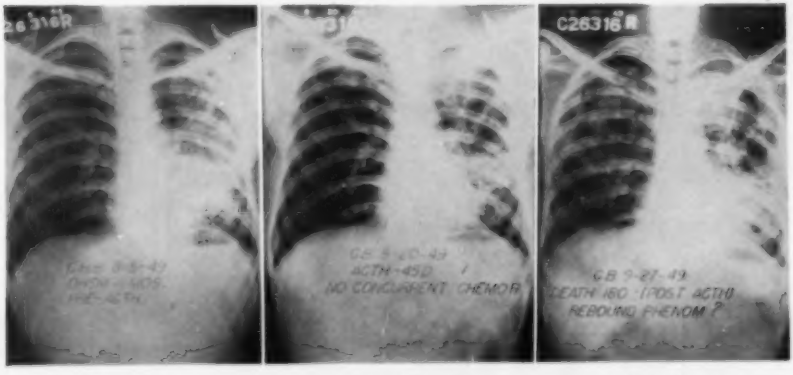

FIGURE 2A FIGURE 2B FIGURE 2C

FIGURE 2: A, B, and C, Case 1 (C. B.). This 29 year old Negro was admitted with far-advanced pulmonary tuberculosis. He received 1.0 gm. of DHSM daily for 30 days before starting on ACTH. Sharp reduction of fever within 24 hours after starting ACTH (see Fig. 1). Dosage of hormone was probably excessive. No concurrent chemotherapy. Serial roentgenograms revealed progression of disease, most marked soon after discontinuing ACTH (rebound phenomenon), and death occurred 18 days later.

Survival: Ten patients died and five survived (3, 7, 9, 12, and 15). Seven of the 10 deaths occurred during, or within four months after discontinuing hormonal therapy. Conversion of sputum did not occur in any case during hormonal therapy. Of the five survivors, three are now living and well (one required thoracoplasty (12), and one thoracoplasty and resection (9) for conversion of sputum and control of disease) and two are still hospitalized, more than four years after hormonal therapy, with far advanced, active pulmonary tuberculosis.

After hormonal therapy, all surviving patients were given chemotherapy of various types and two underwent major chest surgery (9 and 12).

Correlation of Results of Hormonal Therapy with Selected Known Factors

So many factors (known and unknown) differ so much in the few cases reported that correlation of results with any single known factor or group of factors is indeed difficult or impossible. *Age* bore no apparent relationship to the effects of hormonal therapy on tuberculous lesions. *Race*: Four of eight white, and one of six Negro patients survived; and the single Indian died. Thus, white patients fared somewhat better than non-white.

TABLE III

CHEMOTHERAPY AND ROENTGENOGRAPHIC CHANGES FOLLOWING HORMONAL THERAPY

Case No.	Drugs[1]	Duration (Mos.)	X-ray Film Changes	Present Status	
				Status	Mos. after Rx.
1.	DHSM	⅔	Mark. worse	Dead	⅔
2.	DHSM, PAS, TB-1	31	Mod. worse	Dead	31
3.	DHSM + PAS	7	Mark. improv.	L. & W.	56
4.	TB-1	2	Mark. worse	Dead	2
5.	.....	....	.....[2]	Dead	....
6.	SM + PAS, TB-1	4½	Mark. worse	Dead	4½
7.	DHSM + PAS	3	No change	Active TB	53
8.	SM + PAS, TB-1	3½	Mark. worse	Dead	7½
9.	TB-1, SM + INH	25	Mark. improv.[3]	L. & W.	50+
10.	SM + PAS	6½	Mark. worse	Dead	6½
11.	SM	1	Mark. worse	Dead	4
12.	SM + PAS + INH	24	Mark. improv.[3]	L. & W.	50+
13.	.....	....	.....[2]	Dead	....
14.	.....	....	.....[2]	Dead	....
15.	SM + PAS + INH	50	Sl. improv.	Active TB	50

(1) See footnote (1) of Table I.
(2) Died during hormonal therapy. Case 13 died of TB meningitis.
(3) Thoracoplasty done in both cases; also resection in Case 9.

Stage of Disease: The single moderately advanced case did well. As is generally true of tuberculosis, with or without hormonal or chemotherapy, the more advanced and extensive disease the worse the prognosis. The same may be said in reference to the *size and extent of cavitation*. However, we are convinced that hormonal therapy resulted in increased cavitation, spread of disease, or both, in a substantial number of our cases. The relationship of hormonal therapy and the *roentgenographic course of the disease before hormonal therapy* was not clear. Of the five patients surviving to date, roentgenographic changes before hormonal therapy revealed improvement in two, progression in two, and one was started on hormonal therapy shortly after admission.

Duration of chemotherapy before hormonal therapy did not seem to influence the survival rate since exactly one-third survived whether they had received no chemotherapy (one of three), 14 to 28 days of chemotherapy (one of three), or more than one month of chemotherapy (three of nine). Before hormonal therapy, *complete bacillary resistance* to 10 mcgs. of streptomycin per ml. was found in six cases and two survived; partial resistance in four and one survived; and susceptibility tests were not available in five cases (two of the five survived) (Table I). Of the latter five cases, three had received no prior chemotherapy, one received streptomycin for 14 days and another for 28 days. Tests for bacillary susceptibility to PAS were not available in any of the 15 cases.

Although 12 of the 15 cases (Table II) received *chemotherapy concurrently with hormonal therapy*, the bacilli of 10 of the 12 were shown to be

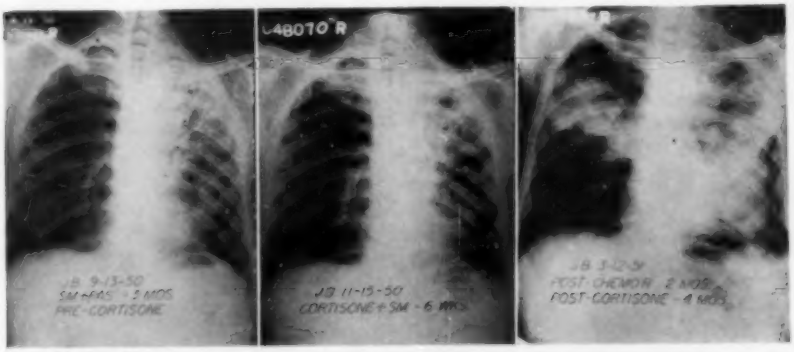

FIGURE 3A FIGURE 3B FIGURE 3C

FIGURE 3: A, B, and C, Case 11 (J. B.). This 44 year old Negro male was admitted with far-advanced pulmonary tuberculosis. Before cortisone therapy, his temperature ranged from 100.6-102° F. for five months despite treatment with daily SM plus PAS. He received 200 mgms. of cortisone for 10 days, 100 mgms. for nine days, 50 mgms. for eight days, and 25 mgms. for 11 days. His temperature reached approximately normal levels at the end of the first week of cortisone therapy, remained near normal while receiving 100 mgms. daily, but "escaped" when the dosage of cortisone was reduced to 50 mgms. and thereafter spiked to 102-103° F. He received daily SM plus PAS concurrently with cortisone but this did not represent effective chemotherapy since his bacilli were completely resistant to streptomycin before cortisone was started. Serial roentgenograms revealed slight progression of disease during cortisone therapy, and death occurred four months after it was stopped.

totally or partially resistant to streptomycin before hormonal therapy, and two (3 and 12) were not tested. One (12) of the latter two had received 1.0 gm. of streptomycin daily for two weeks before cortisone was added for a 31 day period; and he subsequently underwent thoracoplasty and recovered. The other (3) was the *only one* of all 15 cases who fulfilled both of the following conditions: (1) he did not receive antituberculous drug therapy prior to hormonal therapy, and (2) he did receive his "original" course of chemotherapy concurrently with hormonal (ACTH) therapy (Table II) (Fig. 4). This patient made an uneventful recovery and is now well. However his bacilli were not tested for susceptibility to the drug (dihydrostreptomycin) used.

Of the 10 who received ACTH, seven died and three survived. Roentgenographic changes during ACTH therapy revealed improvement in two (3 and 7) and progression in eight cases. Of three treated with *cortisone*, two died and one survived. During cortisone therapy, roentgenographic worsening was observed in two cases and none improved. The sole survivor (12) showed no change during cortisone therapy but subsequently recovered following prolonged chemotherapy and thoracoplasty. Two (14 and 15) received *both hormones* consecutively and one survived. Roentgenographic worsening was observed in both cases during hormonal therapy.

It is interesting to note that the maximum 24-hours excretion of 17-

TABLE IV

SELECTED PHYSIOLOGIC EFFECTS OF HORMONAL THERAPY IN FIFTEEN PATIENTS WITH PULMONARY TUBERCULOSIS

Case No.	Initials	Blood Pressure (m.m. Hg.) B	D	Fasting Blood Sugar (mg. %) B	D	24 Hr. Excretion 17-Ketost. (Mgs. per 24 Hrs.) B	D	Concurrent Daily Dosage of Hormone
1.	C. H. B.	116/84	164/100	60	205	15.0	109.9	ACTH 100 mg.
2.	W. F.	110/70	176/120	75	138	6.8	106.0	ACTH 100 mg.
3.	C. D.	100/76	144/110	84	103	14.8	50.0	ACTH 100 mg.
4.	J. C. D.	110/80	140/102	88	....	7.3	22.5	ACTH 40 mg.
5.	M. T.	84/40	94/66	76	83	5.3	13.8	ACTH 40 mg.
6.	C. B.	108/76	138/100	88	260	17.0	28.0	ACTH 40 mg.
7.	J. D.	92/68	150/100	84	94	9.1	37.4	ACTH 40 mg.
8.	J. L.	100/74	180/120	86	....	20.7	52.0	ACTH 40 mg.
9.	F. E.	115/80	140/100	70	112	12.0	37.0	ACTH 40 mg.
10.	M. C.	106/70	110/90	83	108	....	....	Cortisone 100 mg.
11.	J. B.	104/76	128/92	60	70	....	....	Cortisone 100 mg.
12.	R. M.	126/88	145/106	73	68	....	....	Cortisone 40 mg.
13.	P. P.	110/70	124/80	92	98	14.0	56.0	ACTH 80 mg.
14.	J. F.	116/70	114/88	97	115	6.0	26.0	ACTH 40 mg.
15.	J. M.	108/70	170/112	91	159	12.0	51.0	ACTH 40 mg.

*Before (B) and during (D)—ACTH therapy (Maximum values).

ketosteroids during ACTH therapy was less than 30 mgms in four cases (4, 5, 6 and 14) and none survived; whereas eight of the 12 ACTH-treated cases excreted more than 35 mgms. daily and four survived (3, 7, 9 and 13).

One may wonder whether or not poor results should be wholly charged to deleterious effects of ACTH in patients who show little if any evidence of physiologic response (as measured by the quantity of 17-ketosteroids excreted in the urine during 24-hour periods) to the dosages given. Physiologic effects of ACTH must vary with the patient's general condition, ability to respond (including the physiologic integrity and responsiveness of target organs and cells), and the dosage and duration of hormonal therapy.

Complications (Side Effects)

A complete discussion of the many metabolic and physiologic effects of ACTH and cortisone is beyond the scope of this report. A few of these effects were selected and recorded in Table IV.

Diastolic and systolic blood-pressures were moderately to substantially elevated by ACTH therapy in all but two patients (5 and 14); both of whom were critically ill, emaciated, and died during hormonal therapy. A typical response was a rise of blood-pressure from 110/76 to 144/110 (3). ACTH therapy resulted in elevation of fasting blood-sugar levels in the majority of cases and exceeded 200 mgs. per cent in two cases (1 and 6). Glucose tolerance tests resulted in a diabetic-type of curve in several cases. Electrolyte patterns revealed some lowering of serum potassium levels in all cases; and serum sodium and chloride levels varied much less, and less consistently.

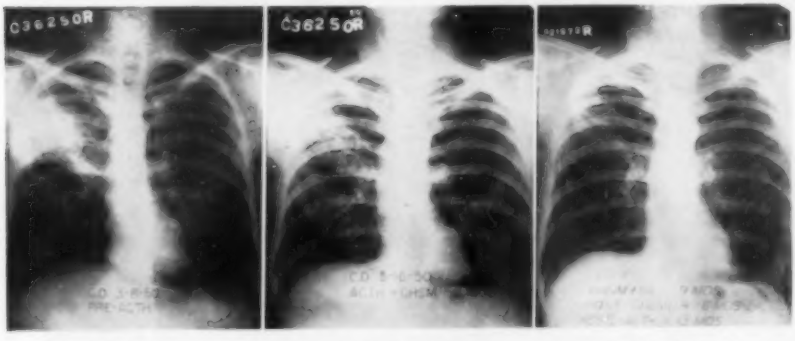

FIGURE 4A FIGURE 4B FIGURE 4C

FIGURE 4: A, B, and C, Case 3 (C. D.). This 45 year old white male was admitted with acute pneumonic tuberculosis and his temperature ranged from 102-104° F. Two weeks after admission he was started on treatment with ACTH plus DHSM daily. Temperature dropped from 104° F. to normal within 24 hours after starting ACTH; and remained normal. The dosage of ACTH was 100, 80 and 60 mgms. for successive five day periods; 40 mgms. for nine days, and 20 mgms. for the remainder of a 62-day period of ACTH therapy. In this case, the dosage of hormone was properly reduced to less dangerous levels early in the course of treatment; and he concurrently received 1 gram of streptomycin daily. Serial roentgenograms revealed slight improvement two months after treatment was started. After discontinuation of hormonal therapy, he received DHSM plus PAS daily for seven months and serial x-ray films revealed marked improvement. He is now living and well.

Hormonal therapy resulted in elevation of CO_2 combining-power in most cases; and this reached 34 to 48 meq. (75 to 105 Vol. per cent) in 10 of the 12 patients treated with ACTH. One patient (7) developed marked edema, ascites and pleural effusion coincident with laboratory evidence suggesting hypochloremic hypokalemic alkalosis. His condition became critical but he responded quickly following intravenous administration of potassium chloride and omission of ACTH for two days only. It was this case that led us to substitute KPAS for NaPAS in patients receiving hormonal therapy

Discussion

The effects of ACTH cortisone on tuberculous lesions may vary with many factors including: (1) the different species of infected hosts, and whether or not they were previously sensitized to tuberculin; (2) the physiologic status of the infected host (nutritional status e.g. starvation or post-gastric resection in man, presence and severity of diabetes mellitus, age, sex, etc.); (3) the functional state of target organs and tissue cells; (4) the type, timing, dosage, frequency and mode of administration, and duration of hormonal therapy;(5) which combination of antimicrobial drugs are given, their dosages, frequency of administration and duration of therapy, and whether or not these drugs are given before, concurrently with, and/or following hormonal therapy; (6) whether the antimicrobial therapy represents an "original" course of treatment, or re-treatment for a drug-susceptible or drug-resistant infection (completely drug-susceptible or drug-resistant organisms); (7) duration, stage and dynamic status of the disease (minimal versus far-advanced, reversible inflammatory versus irreversible destructive disease, actively progressing versus stable inactive disease, or disease of recent onset versus long duration); (8) whether the antimicrobial drug diffuses freely into the cells, caseous foci, cerebrospinal fluid, etc. as does isoniazid in contrast to streptomycin and PAS (Lurie and others reported that multiplication of the intracellular tubercle bacilli was enhanced by administration of cortisone, and many antimicrobial drugs have been most effective against actively multiplying bacilli); and (9) other known and measurable factors as well as many unknown and immeasurable host-factors. When one considers the complex variety of combinations of the multitude of known and unknown factors in the various species and individual hosts treated, the existing controversy concerning the effects of ACTH and cortisone in tuberculous infections is not surprising.

Whereas most authorities report harmful effects from the use of cortisone or ACTH in the presence of tuberculous infections,[1-22] other reliable investigators report equivocal or no harmful effects from normal dosages of cortisone or relatively high dosages of ACTH.[23-34] Several reports suggest that the potentially deleterious effects of hormonal therapy may be neutralized by concurrent administration of effective antimicrobial therapy.[10, 17, 18, 29, 33, 42, 43]

In rabbits, Smith and his associates found that high, or even normal, dosages of cortisone often had deleterious effects upon tuberculous lesions;

whereas ACTH had no harmful effect unless given in dosages exceeding seven to 20 times the normal range. They reported that concurrent streptompycin therapy neutralized the potential ill-effects of cortisone in dosages up to two to six times normal, and of ACTH in dosages as high as 20 times normal. The inflammatory reaction ordinarily produced by the introduction of tuberculin into the lungs of previously sensitized rabbits, was substantially reduced by ACTH.[28]

Some observers[42, 43] report that ACTH or cortisone with concurrent chemotherapy was more effective than chemotherapy alone in certain cases of pulmonary tuberculosis. Houghton[42] found ACTH particularly helpful in patients who were in urgent need of anti-tuberculous drug therapy and who manifested marked hypersensitivity or intolerance to these drugs. We[58] and others[59, 60] have successfully used ACTH in an occasional patient who was extremely hypersensitive to streptomycin, PAS, and isoniazid.

Many case reports[48-56] and personal communications attest to the dangers of reactivation of latent tuberculosis, progression of active tuberculosis, or development of miliary or meningeal tuberculosis among patients treated with ACTH or cortisone for various conditions such as the collagen diseases and rheumatoid arthritis. However, some of the case reports do not clearly exclude the presence of active pulmonary tuberculosis before hormonal therapy was started since adequate chest roentgenograms were not taken.

Addison's disease coexisting with tuberculosis is properly treated by replacement therapy (cortisone or hydrocortisone) given concurrently with effective anti-tuberculosis drugs.[35, 45, 47] With proper dosage, the blood-level of these hormones may be restored to nearer normal levels rather than grossly exceeding them. When tuberculosis coexists with conditions presenting urgent indications for hormonal therapy, such as systemic lupus erythematosus, polyarteritis nodosa etc. (particularly when the latter conditions are more threatening to life than is the associated tuberculosis) a trial of ACTH with concurrent intensive antimicrobial therapy seems indicated.

Ten of the 15 cases, included in this report, were shown to be completely or partially resistant to streptomycin before receiving hormonal therapy, and bacillary susceptibility tests were lacking in five (1, 2, 3, 10, and 12). (See background factors and correlation of results of hormonal therapy—Tables I and II). Of the latter five cases, two (1 and 12) received chemotherapy for 28 and 14 days respectively prior to hormonal therapy; and two (2 and 10) did not receive chemotherapy concurrently with hormonal therapy. Thus, *only one* (3) of the 15 cases met both conditions of not receiving anti-tuberculosis drug therapy before receiving hormonal therapy, and receiving his "original" course of chemotherapy concurrently with hormonal therapy; but bacillary susceptibility tests were not available in this case. Consequently results in this group of cases were, in general, not pertinent to the question of whether ACTH (or cortisone) would be beneficial or harmful in "original-treatment" drug-susceptible cases of

tuberculosis when given concurrently with the original course of anti-tuberculosis drug therapy.

Exclusive of all other variable factors (known and unknown), the effects of concurrent hormonal and chemotherapy in tuberculous patients who had previously received considerable chemotherapy and whose bacilli were highly resistant to the antimicrobial drugs given, (as was true in the majority of our cases), cannot be validly compared with effects in patients who receive hormonal therapy concurrently with their "original" course of effective chemotherapy. Usually streptomycin is not effective chemotherapy for a patient whose bacilli are completely resistant to the drug.

We do not recommend the use of hormonal therapy in previously treated tuberculous patients whose bacilli are completely resistant to the anti-tuberculosis drugs available unless hormonal therapy is mandatory and there is no other alternative. We are most reluctant to use hormonal therapy for the usual case of pulmonary tuberculosis. However, as noted above, the contraindications may be relative rather than absolute and, in certain circumstances, advantages may outweigh disadvantages. We do believe the potential ill effects of hormonal therapy given alone, or with chemotherapy in re-treatment drug-resistant cases, may be substantially reduced if not completely neutralized in "original-treatment" drug-susceptible cases by concurrently giving effective anti-tuberculous drugs (preferably including isoniazid as one of the two or more drugs given). For reasons previously stated, results in the case material presented can add little evidence to support this impression.

In addition to chemotherapy, ACTH and cortisone have been recommended for the treatment of tuberculous meningitis,[37-41] particularly in those cases with evidence of impending or actual subarachnoid block. The need for hormonal therapy in tuberculous meningitis has seemed limited in our experience. Since starting triple drug (streptomycin plus PAS plus isoniazid) in early 1952, 20 of 22 consecutive patients with tuberculous meningitis have survived and appear to be well one and a half to three years after the start of treatment. The two fatalities occurred on the 11th day, and 17 hours after admission. None of the 22 developed evidence of subarachnoid block. When death appeared to be imminent soon after starting treatment in a child seen at another hospital, we recommended the addition of ACTH in the hope of prolonging life until triple drug therapy would have sufficient time to exert its maximum therapeutic effect. Subsequent survival in this case could not be credited to the addition of ACTH with any certainty since we were not sure that death would have otherwise ensued.

SUMMARY

The effects of ACTH and cortisone in 15 cases of pulmonary tuberculosis are presented.

In the cases reported, cortisone was usually harmful and never beneficial; whereas ACTH may have been beneficial in an occasional case, of equivocal effect in some, and probably harmful in the majority.

Contraindications to hormonal therapy in tuberculosis seem to be relative rather than absolute; and, in special circumstances, advantages may out-weigh disadvantages.

When hormonal therapy is mandatory in the presence of tuberculosis, and a choice of either ACTH or cortisone is available, preference should be given to ACTH. Effective antimicrobial therapy must always be given concurrently in an effort to neutralize or minimize the potential ill-effects of hormonal therapy insofar as is possible; and hormonal therapy discontinued in step-wise fashion as rapidly as the patient's condition permits.

RESUMEN

Los efectos de ACTH y cortisona en 15 casos de tuberculosis pulmonar, se presentan.

En los casos relatados la cortisona fué habitualmente daño sa y nunca benéfica; en tanto que ACTH puede haber sido benéfica en algún caso ocasional, de efecto equívoco en algunos y probablemente dañoso en la mayoría.

Las contraindicaciones para la terapia hormonal en tubeculosis, parecen ser más bien relativas que absolutas; y en circunstancias especiales, las ventajas pueden sobrepasar a las desventajas.

Cuando es imperativa la terapia hormonal en presencia de tuberculosis y ha de escogerse entre ACTH y cortisona, debe preferirse la primera.

La terapéutica antimicrobiana debe siempre darse al mismo tiempo para neutralizar o disminuir el mal efecto de la terapia hormonal en lo posible; y la terapia hormonal ha de suspenderse a pasos discretos una vez que las condiciones del enfermo lo permitan.

ZUSAMMENFASSUNG

Die Wirkungen von ACTH und Cortison bei 15 Fällen von Lungentuberkulose werden vorgelegt. In den dargestellten Fällen war das Cortison gewöhnlich schädlich und niemals nützlich; ACTH dagegen war in einem gelegentlichen Falle nützlich, von zweifelhafter Wirkung in manchen Fällen und in der Mehrzahl wahrscheinlich schädlich.

Kontraindikationen gegen eine Hormonbehandlung bei der Tuberkulose scheinen mehr relativ als absolut zu sein; und unter besonderen Umständen können die Vorteile die Nachteile überwiegen.

Wenn eine Hormonbehandlung bei Vorliegen einer Tuberkulose zwingend notwendig und eine Wahl zwischen ACTH oder Cortison möglich ist, sollte man dem ACTH den Vorzug geben. Eine wirksame antimikrobielle Therapie muss immer gleichzeitig erfolgen in dem Bemühen, die potentiellen üblen Nebenwirkungen der hormonellen Therapie so weit wie möglich zu neutralisieren oder zu verringern; und die hormonelle Therapie muss schrittweise abgesetzt werden, sobald es irgend der Zustand des Kranken zulässt.

References omitted due to space limitations. A complete list of references may be obtained from the authors upon request.

Pathogenesis of Cardiac Rupture Due to Myocardial Infarction

A Study of Twenty-Six Cases

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Introduction

Cardiac rupture is an infrequent complication of myocardial infarction, occurring in from 4 to 9 per cent of cases of acute myocardial infarction in necropsy series.[1-4] Factors considered important in its etiology have been heavy leukocytic infiltration in the area of infarction[2, 5] involvement of the full thickness of the wall by infarction, fatty infiltration into the myocardium;[5] absence of fibrosis,[5] and persistence of hypertension or undue exertion by the patient during the acute post infarction period.[7]

We have noted these conditions occurring in many cases of myocardial infarction without rupture, and therefore question their etiological significance. Infiltrating intramural hemorrhage has been mentioned in the literature[8, 9] but its importance has not been stressed. Therefore, we considered it worthwhile to study those cases of myocardial infarction with rupture which had been necropsied at Milwaukee County Hospital during the past 13 years for the purpose of examining the etiological significance of the above mentioned factors as well as the potential role of intramural hemorrhage.

Material and Methods

There were 26 cases of myocardial infarction with cardiac rupture among the 6791 necropsies performed at this hospital from 1942 to 1955, an incidence of 0.37 per cent. The 26 cases comprised an incidence of 2.7 per cent of the 970 cases of myocardial infarction necropsied here during the same period.

Clinical Data

Of the 26 cases, 16 occurred in males and 10 in females. The average age at time of death was 70.7 years. Four were psychotic patients. In the cases of rupture the longest recorded survival after onset of symptoms of infarction was eight days. The average length of survival was 4.2 days. In four instances it was not possible to determine the exact time of onset of symptoms because of the patient's mental status. In following the clinical course of patients after infarction, it was noted that blood pressures were below 140/90 millimeters of mercury in 11; between 140/90 and 180/110 millimeters Hg. in six; and above 180/110 millimeters Hg. in four. These

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blood pressure findings did not appear to show any significant elevation above that seen in cases of myocardial infarction without rupture. Bean had the same experience in his cases of myocardial infarction with rupture.[4] There was no clinical history of previous myocardial infarction in any case.

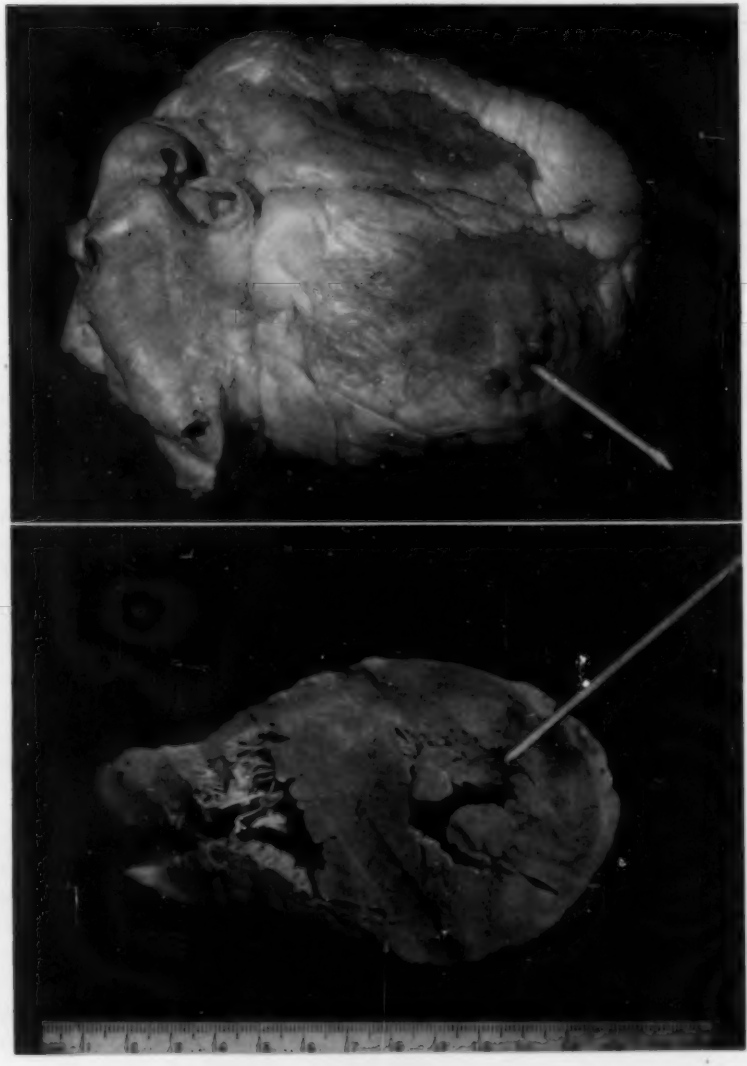

FIG. 1A

FIG. 1B

Figure 1A: Site of perforation in posterior wall of right ventricle marked by applicator stick extending from it. Note narrow zone of hemorrhage surrounding torn epicardium.—*Figure 1B:* Applicator stick passing through tract of rupture shown above. Note the zone of intramural hemorrhage surrounding tract.

Pathologic Findings

Gross Findings: The heart was weighed in 20 cases. The average weight was 453 grams, with the following distribution of weights: 300 to 400 grams, seven cases; 400 to 500 grams, seven; 500 to 600 grams, four cases; and greater than 600 grams, in two. The area of infarction was of moderate or large size in 22 and small (less than 3 centimeters in diameter) in four. The site of coronary occlusion was identified in 19, and the cause of occlusion was thrombosis in 18 and arteriosclerosis in one. In 12 cases (63.0 per cent) the site of occlusion was the left descending branch of the left coronary artery; in three (16 per cent) the site was the circumflex branch of the left coronary artery; and in four (21 per cent) it was the right coronary artery.

The site of rupture in all cases was within the area of infarction. In 23 cases identification of the site of rupture included at least which wall was ruptured. The site of rupture was in the anterior wall of the left ventricle in 14 (61 per cent), in the posterio-lateral wall of the left ventricle in five (22 per cent), the posterior wall of the left venrticle in one, the anterior wall of the right ventricle in one, and the interventricular septum in two. In only one was there a scar of a previous myocardial infarction; in this case the scar was 3 cm. away from the site of fresh infarction and rupture. The exact site of rupture was recorded as follows: anterior wall of the left ventricle near the apex, six cases; the anterior wall of the left ventricle midway along the course of the left descending coronary artery, two; posterio-lateral wall of left ventricle midway between the base and the apex, one (Figure 1); near the center of the posterior wall of the left ventricle, one; lateral wall of the left ventricle near the atrio-ventricular groove, one; midway between the apex and base, one; anterior wall of the right ventricle near the apex, one; and the interventricular septum, 1 centimeter above the apex, one. The site of rupture consisted of a linear tear which ranged in length from 4 millimeters to 3 centimeters. In two the site of rupture contained more than one tear, two tears in one, and three in the other.

Histologic Findings: The histological changes to be described are those found at and near the site of rupture.

Necrosis in 10 cases was far advanced with complete destruction of many fibers and large amounts of necrotic debris from myocardial fibers and inflammatory cells. In adjacent areas myocardial fibers showing loss of all cytoplasmic detail and nuclei often remained. Necrosis appeared complete except for autolysis. In necrotic areas with autolysis there was a heavy infiltration by histiocytes. In those areas without autolysis there was little inflammatory infiltration.

In six cases necrosis was moderately advanced. Myocardial fibers with karyorrhectic or pyknotic nuclei persisted. In the remaining seven the myocardial fibers were barely altered; cytoplasm was slightly swollen, striations were slightly obscured and nuclei were quite often slightly pyknotic.

Necrosis involved the full thickness of the wall in 15, two-thirds of the thickness in seven, and one-third of the wall in one.

Infiltration by granulocytes and histiocytes around the area of perforation was considerable in six, moderate in 10, and slight in six. In those with advanced necrosis, degree and type of exudation varied considerably. Where necrotic fibers were disintegrating or had been removed, there were collections of partially or completely necrotic neutrophilic granulocytes and macrophages. Where large areas of dead myocardial fibers persisted, there was almost no exudation. It appeared that autolysis of the dead fibers had failed. Nevertheless, the outlines of necrotic debris between these fibers suggested that neutrophilic granulocytes had been present. In areas of advanced necrosis its degree usually exceeded that of the inflammatory cellular reaction. In areas of moderately advanced necrosis the degree of exudation usually paralleled degree of necrosis, the exudate consisting chiefly of well-preserved neutrophilic granulocytes. Cases with almost no apparent necrosis often had much exudate.

Fibrosis was absent from the vicinity of rupture in all cases. Fatty infiltration was present in 16, usually confined to the outer half of the myocardial wall. The fat was frequently part of the pathway for a dissecting hematoma.

There were thrombi in the Thebesian vessels (including the Thebesian veins, the myocardial sinusoids, arterio-luminal and arteriosinusoidal vessels) in nine. In two they were old enough to show early organization, while in seven they were fresh. In three the thrombi were associated with far advanced necrosis, in the remaining with moderately advanced necrosis. In one of the former, a Thebesian vessel filled with a partially organized thrombus extended outward so far that its wall was separated from the

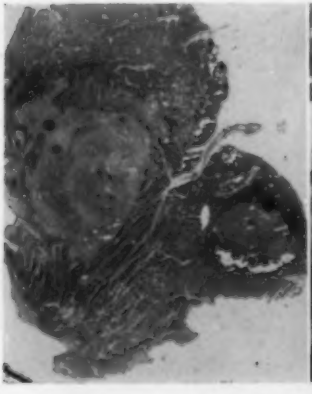

FIGURE 2

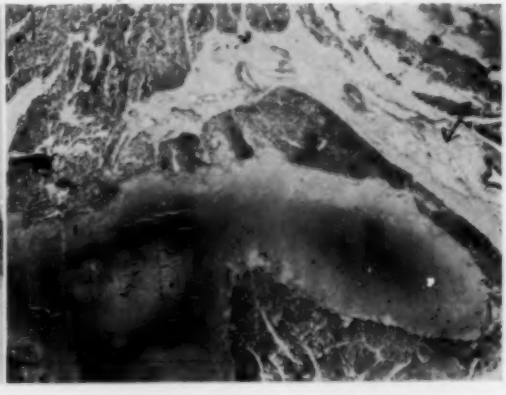

FIGURE 3

Figure 2: Larger hematoma in inner two-thirds of left ventricular wall. Note how it infiltrates between intact myocardial fibers and bundles.—*Figure 3:* Dissecting hematoma which has infiltrated in both a transverse and longitudinal plane. Arrow indicates a projection of the epicardium.

epicardium by a width of only three myocardial fibers. These fibers were hydropic but not ruptured. Another case with moderately advanced myocardial necrosis had a narrow rim of myocardial fibers immediately surrounding a freshly thrombosed Thebesian vessel which showed more recent necrosis and granulocytic exudation than the advanced necrotic tissue outside the rim. Considerable interfibrillar hemorrhage surrounded this thrombotic vessel. These examples suggest that there is a narrow zone around Thebesian vessels which may be partially preserved during infarction because of the blood supplied by the Thebesian vessel and that thrombosis of the Thebesian vessel may cause acute degenerative changes in those surrounding fibers.

Using the histological criteria of Mallory, White, et al,[6] the age of the infarction at the site of rupture was estimated as follows:

	No. Cases
9 - 10 Days	2
7 - 8 Days	3
5 - 6 Days	2
4 - 5 Days	2
3 - 4 Days	2
2 - 3 Days	9
Less than 1 Day	1

FIGURE 4

FIGURE 5

Figure 4: Wedge-shaped hematoma which has bursted directly through necrotic myocardium. Arrows outline margin between myocardium and hematoma.—*Figure 5:* Wedge-shaped hematoma which has infiltrated myocardium and has finally burst through epicardium.

In 17, the histological sections available were such that the path of rupture could be traced. In all of them the path was filled with blood. In these with infarctions over three days old the blood was mixed with varying amounts of granulocytes and necrotic debris and was partially clotted. However, outside the clotted portion was usually a zone of unclotted blood infiltrating the surrounding myocardial fibers. In the cases with infarctions two days old or less, the dissecting hematoma was fresh and unclotted.

In 13, penetration of the wall by the mass of blood was by infiltration of blood through the loose connective tissue and fat located between the muscle bundles and fibers, separating rather than destroying fibers (Figure 2). The pathway was usually oblique and in some sites almost parallel to the wall (Figure 3). In eleven of these cases, the infarction was less than four days old, and in two, five to six days old. In four with infarctions six to 10 days old, penetration was for the most part directly through necrotic areas, and the penetrating hematoma was wedge-shaped, composed of recently clotted blood surrounded by a zone of unclotted blood (Figure 4). However, even in these cases there was considerable infiltration by blood into the interstitial connective tissue.

In most cases the largest mass of blood was in the middle third of the wall and in two surrounded two small arteries, suggesting that these were the source of hemorrhage. In two it could be traced to the wall of a Thebesian vessel lying in the middle one-half of the wall, in which the endothelium was swollen and infiltrated by neutrophilic granulocytes. In a few cases the hematoma could be seen breaking through the epicardium (Figure 5).

Discussion

Etiological factors which have been emphasized considerably are degree and extent of myocardial necrosis and the abundant exudation of neutrophilic granulocytes accompanying it.[2, 5, 6] However, the histological findings in our cases do not bear out the importance of these two factors. In eight, myocardial degeneration was barely detectable. In 13 of 17 in which the pathway of rupture could be studied the penetrating hemorrhage did not pass through necrotic myocardium, but infiltrated between muscle bundles and fibers. De-emphasizing the importance of extent of necrosis through the wall was our finding of only 15 of 23 cases with necrosis of the full mural thickness. In another study one of the authors (JHL) examined 30 infarcted but unruptured hearts and found the degree and extent of necrosis to be greater than in this series of ruptured hearts. The finding of slight or moderate leukocytic infiltration near the site of rupture in 17 and considerable infiltration in only five makes the etiological importance of leukocytic infiltration improbable.

A factor we considered possibly important in cardiac rupture was thrombosis of Thebesian vessels, which are known to be important in myocardial blood supply, especially in regions of infarction caused by coronary arterial occlusion.[11]

It was thought that these vessels might cause necrosis of the narrow

zone of myocardium supplied by them and thereby remove the few viable fibers remaining in the myocardial wall. This thesis was not borne out by our results. First, Thebesian thrombosis was found near the rupture in only nine; and second, although the narrow zone of relatively intact myocardium presumably protected by the Thebesian vessels frequently showed hydropic degeneration when the vessels were thrombotic, there was no sign of rupture.

The pathological change in this series considered to be of major importance in mural rupture was the large hemorrhage within the wall in the vicinity of rupture. This hemorrhage appeared to have been a dissecting one, extending both transversely and longitudinally. In almost all cases penetration was largely by infiltration between myocardial fibers and bundles, the chief pathways being loose connective tissue and fat. In only four, all showing advanced necrosis, did the blood pass directly through necrotic myocardial substance. Even in these there was considerable interstitial infiltration. The source of the infiltrating hemorrhage could not be definitely determined; however, the finding of the largest collections of interstitial blood in the middle and outer thirds of the wall in six of the 16 suggests that in these, at least, the hemorrhage began in the wall. It seems from these findings that the mechanism of rupture is somewhat similar to that which occurs in dissecting aneurysm of the aorta. The counterpart of medical necrosis in the latter condition is the myocardial infarction, both conditions resulting in loss of support and alterations of the wall of small vessels, leading to hemorrhage and the formation of a dissecting mass of blood, propelled by the systemic blood pressure.[12] However, unlike the wall of the aorta which offers rigid resistance to transverse dissection and allows dissection only in the longitudinal plane, the nonfibrotic cardiac wall permits transverse as well as longitudinal dissection within it. By such transverse dissection the point of rupture would consist only of a mass of blood surrounded by the easily penetrable endocardium and pericardium.

None of the cases in this series received anti-coagulant therapy. Nevertheless, it is conceivable that the greater tendency to intramural hemorrhage could account for the greater incidence of myocardial rupture reported in cases of myocardial infarction treated with anti-coagulant.[13]

One would have to seriously question whether dissecting intramural hemorrhage is the main cause of hemorrhage in all cases of myocardial infarction with rupture, for it has been stressed in so few of the reported cases. However, since the area of the dissecting hemorrhage in our cases was frequently narrow, one could easily ignore or overlook its significance. Perhaps one important point in favor of its importance is that it is one of the few considered etiological factors which is rarely found in myocardial infarction without rupture.[14]

SUMMARY AND CONCLUSIONS

1. A clinical and pathological study was made of 26 cases of myocardial infarction with rupture.

2. Their average age was 70.5 years. There were 16 males and 10 females. There was no previous history of infarction in any case. Based upon histological study, the age of the infarct at the time of rupture was less than two weeks in all, less than one week in 19, and less than three days in ten.

3. Etiological factors such as hypertension, over-exertion, fatty infiltration and granulocytic exudation were not found to be of particular significance in this series.

4. A factor considered in our series to be important in the cause of cardiac rupture in myocardial infarctions was penetration of the wall by a dissecting hematoma. Such a hematoma was found in a majority of cases. In a substantial number blood penetrated the wall by infiltration in the loose interstitial tissue between intact myocardial fibers. In a few the hematoma penetrated mainly through necrotic myocardial fibers. An analogy is drawn between the mechanism of this dissecting hematoma and that found in dissecting aortic aneurysm.

RESUMEN

1. Se estudiaron 26 casos de infarto del miocardio con ruptura, desde los puntos de vista clínico y anatomopatológico.

2. El término medio de edad fué de 70.5 años. Fueron 16 hombres y 10 mujeres. No había antecedentes de infarto previo en ninguno de ellos. Basándose en el estudio histológico la edad del infarto al momento de la ruptura era menos de dos semanas en todos, menos de una semana en 19 y menos de tres días en 10.

3. No se ha encontrado que tuviesen significación particular en esta serie factores etiológicos como la hipertensión, exceso de actividad física, infiltración grasosa, o exudación granulocítica.

4. Un factor que se consideró en nuestra serie como importante en la ruptura cardiaca en el caso de infarto fué la penetración de la pared por un hematoma disecante. Tal hematoma se encontró en la mayoría de los casos. En un número importante la sangre penetró por infiltración en el tejido laxo intersticial entre fibras intactas del miocardio. En un poco, el hematoma penetró principalmente a través de fibras miocárdicas en necrosis. Se estable ce analogía entre el mecanismo de este hematoma disecante y el encontrado en el aneurisma disecante de la aorta.

ZUSAMMENFASSUNG

1. Es wurde eine klinische und pathologische Untersuchung angestellt an 26 Fällen von Myocard-Infarktbildung mit Ruptur.

2. Ihr Durchschnittsalter betrug 70,5 Jahre. Es waren 16 Männer und 10 Frauen. In keinem Fall bestand eine Vorgeschichte hinsichtlich Infarktbildung. Ausgehend von der histologischen belief sich das Alter des Infarktes z. Zt. der Ruptur in allen Fällen auf weniger als 2 Wochen, auf weniger als 1 Woche in 19 Fällen und weniger als 3 Tage in 10 Fällen.

3. Solche aetiologischen Faktoren wie Bluthochdruck, Überanstrengung, fettige Infiltration und granulocytäre Exsudation wurden nicht als von

besonderem Belang in dieser Untersuchungsreihe gefunden.

4. Als ein in unserer Untersuchungsrihe wichtiger Faktor für die Ursache von cardialen Rupturen bei Herzmuskel-Infarktibildung wurde die Durchsetzung der Wand mit einem intramuralen Haematom angesehen. Ein solches Haematom wurde in der Mehrzahl der Fälle gefunden. In einer beträchtlichen Anzahl durchdrang das Blut die Wand mittels Infiltration des lockeren interstitiellen Gewebes zwischen intakten Herzmuskelfasern. In wenigen Fällen drang das Haematom hauptsächlich durch nekrotische Herzmuskelfasern. Eine Parallele wiwrd gezogen zwischen dem Mechanismus eines intramuralen Haematoms und demjenigen, das man beim intramuralen Aortenaneurysma findet.

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Ambulatory Treatment of Tuberculous Intrathoracic Lymphadenitis*

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Since July 1953, the Bedford Chest Clinic, one of the 23 clinics of the Bureau of Tuberculosis, New York City Department of Health, has participated in the city-wide program of giving chemotherapy to non-hospitalized patients with active or recently active tuberculosis.[1] All clinic patients with active tuberculosis were routinely referred by the clinic physicians for hospitalization. Those patients with active disease who refused hospitalization were treated at the clinic. Approximately 350 have been started and continued on treatment. Among them were nine with tuberculous intrathoracic lymphadenitis which we wish to report.

Selection of Patients

This group had unilateral intrathoracic lymph node disease without tuberculous parenchymal lung involvement as shown by posteroanterior and lateral projections of the roentgenograms. All were over 10 years of age, the average being 19 years. All were Negroes. The skin reactions were positive to tuberculin in each case. One had positive sputum cultures and another with a small cervical lymph node showed tuberculosis on biopsy. History, physical examination, sputum or laryngeal swab cultures, blood studies, and where indicated, tomograms, bronchoscopy and biopsies of peripheral lymph nodes failed to reveal other etiologies of the enlarged intrathoracic lymph nodes.

Although the tuberculous etiology was proved in only two of the nine patients before treatment was started and in another after resection, we have little doubt as to the tuberculous etiology in the entire group.

Method of Treatment

All patients were placed on a basic regimen of isoniazid, 5 mgm. per kilo, and para-aminosalicylic acid, 12 grams daily for adults. If PAS was not tolerated, streptomycin—1 gram twice weekly—was substituted. They were advised to follow a prescribed rest regimen, but in most cases home conditions were such that this could rarely be carried out. All had monthly chest roentgenograms and cultures of sputum, laryngeal swabs or gastric contents. All have been continued on chemotherapy up to the time of this writing with the exception of Case 7.

Response to Treatment

Seven of the nine patients showed marked regression or complete disappearance of the enlarged intrathoracic lymph nodes within two to four

*From the Bedford Chest Clinic of the Bureau of Tuberculosis, New York City Department of Health.

TABLE I
RESPONSE OF INTRATHORACIC TUBERCULOUS LYMPHADENITIS TO CHEMOTHERAPY

Patient	Age	Sex	Size and Site of Nodes at Discovery	Therapy	Time Interval for Marked Improvement or Disappearance	Duration of Follow-Up Subsequent to Start of Clinic Treatment	Remarks
1. L.B.	23	M	2 Plus. Right hilar.	INH PAS	2 months	14 months	
2. H.K.	32	M	2 Plus. Right paratracheal and hilar.	INH PAS	4 months	13 months	Intrathoracic lymphadenitis existed for 15 mos. unchanged before therapy. Biopsy cervical node tuberculous
3. G.R.	27	F	3 Plus. Left hilar.	INH Streptomycin	1½ months	6 months	Bronchoscopy neg. Ca considered because of symptoms and x-ray appearance
4. J.S.	15	F	3 Plus. Right paratracheal and hilar.	INH PAS	2 months	11 months	Primary complex five years previously healed spontaneously in one year
5. E.D.	14	F	3 Plus. Right paratracheal and hilar.	INH PAS	3 months	11 months	Tomograms showed no evidence of lymphadenitis after three months of therapy
6. G.B.	29	M	3 Plus. Right hilar.	INH PAS	3 months	12 months	Three positive sputum cultures. Converted to negative two months following therapy
7. M.H.	11	F	2 Plus. Left hilar.	INH Streptomycin	3 months	19 months	Stopped therapy after 14 months of treatment
8. A.D.	12	F	3 Plus. Right hilar.	INH PAS	10 months	19 months	Intrathoracic lymphadenitis existed for at least two years unchanged before therapy
9. L.E.	14	M	2 Plus. Right hilar.	INH Streptomycin	No response after 10 mos. of treatment	15 months	Scalenous node biopsy showed chronic lymphadenitis. Surgical removal of hilar node after 10 months showed tuberculous caseation necrosis. Bacteriological confirmation not obtained

Size of Nodes: 1 plus: slightly enlarged
2 plus: moderately enlarged
3 plus: markedly enlarged

months of treatment. The eighth showed considerable regression of the enlarged intrathoracic lymph node after 10 months and complete regression after 15 months. The ninth failed to show regression after 10 months in the clinic and during subsequent hospitalization. The enlarged intrathoracic lymph node was then resected. The pathological specimen showed tuberculous caseation necrosis. During the entire period of observation, none of the nine patients developed clinical or roentgenographic evidence of tuberculosis of any other organ. Further details are noted in Table I.

Discussion

The rapidity of regression of the enlarged intrathoracic lymph nodes in this group of ambulatory treated cases, in the authors' experience, has

FIGURE 1A FIGURE 1B

Figure 1A (Case 2, H.K.): Before therapy. Enlarged right paratracheal and hilar lymph nodes.—*Figure 1B* (Case 2, H.K.): Four months after therapy.

FIGURE 2A FIGURE 2B

Figure 2A (Case 3, G.R.): Before therapy. Enlarged left hilar lymph nodes.—*Figure 2B* (Case 3, G.R.): One and one-half months after therapy.

not been seen prior to the use of isoniazid. It is this anti-microbial agent which seems to be most responsible for the therapeutic results. It is impossible to determine to what extent the results of this small group of patients with tuberculous intrathoracic lymphadenitis is representative of the general trend until larger groups of patients are reported. Our findings seem to be of sufficient significance, however, to warrant the suggestion that a diagnostic trial of isoniazid with PAS or streptomycin for a period of three to four months may be justified in a patient with obscure unilateral interathoracic lymphadenopathy when, in the presence of a positive tuberculin test, all other attempts to establish the etiology short of exploration have failed.

SUMMARY

Nine patients with intrathoracic tuberculous lymphadenitis were treated in the Bedford Chest Clinic with isoniazid in conjunction with PAS or

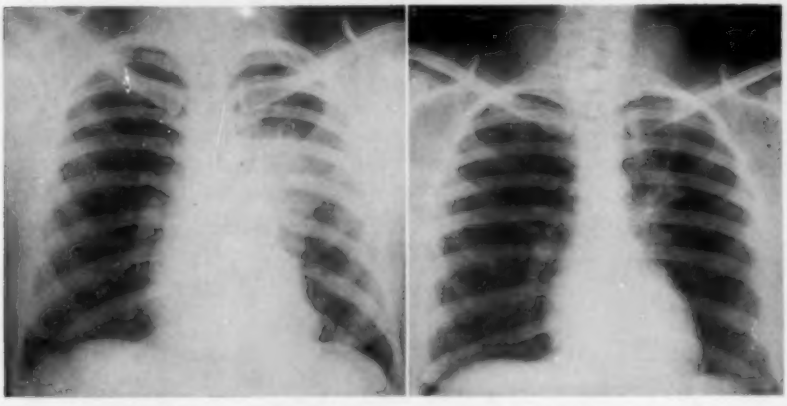

FIGURE 3A FIGURE 3B

Figure 3A (Case 4, J.S.): Before therapy. Enlarged right paratracheal and hilar lymph nodes.—*Figure 3B* (Case 4, J.S.): Two months after therapy.

FIGURE 4A FIGURE 4B

Figure 4A (Case 5, E.D.): Before therapy. Enlarged right paratracheal and hilar lymph nodes.—*Figure 4B* (Case 5, E.D.): Three months after therapy.

streptomycin. Marked regression of the lymphadenitis was observed in the majority (seven out of nine) within two to four months. The results were of sufficient significance to warrant the suggestion of a diagnostic trial of anti-mycobacterial treatment in patients with obscure unilateral intrathoracic lymph node disease in the presence of a positive tuberculin skin test.

RESUMEN

Nueve enfermos de linfadenitis tuberculosa intratorácica se trataron en la Clínica de Tórax de Bedford usando isoniacida combinada con PAS o estreptomicina. En la mayoría se notó marcada regresión de la linfadenitis (siete de nueve) dentro de dos a cuatro meses. Los resultados fueron suficientemente destacados para permitir el uso del tratamiento antimicrobiano como prueba diagnóstica en los enfermos una afección intratorácica de adenitis de etiología obscura, con tuberculino reacción positiva.

RESUME

Neuf malades atteints d'adénopathies tuberculeuses intrathoraciques furent traités à la Clinique Pulmonaire de Bedford par l'isoniazide associé au P.A.S. ou à la streptomycine. Une régression notable de l'atteinte ganglionnaire fut observée dans la majorité des cas (7 sur 9) en deux à quatre mois. Les résultats furent suffisamment frappants pour légitimer l'épreuve thérapeutique pour le diagnostic des adénopathies intrathoraciques d'origine indéterminée, associées à une réaction tuberculinique positive.

ZUSAMMENFASSUNG

9 Patienten mit intrathorakaler Lymphdrüsentuberkulose wurden in der Bedford Chest Clinic mit Isoniazid in Kombination mit PAS oder Streptomycin behandelt. Deutliche Rückbildung der Lymphdrüsenerkrankung wurde in 7 von 9 Fällen innerhalb von zwei bis vier Monaten gesehen. Die Ergebnisse waren derart, dass eine tuberkulostatische Therapie zu diagnostischen Zwecken bei Patienten mit einseitiger intrathorakaler Lymphknotenerkrankung unklarer Genese vorgeschlagen werden kann, vorausgesetzt, dass die Tuberkulin-Reaktion positiv ist.

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The Paulino Thoracoplasty

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At the annual meeting of the American Association for thoracic surgery at Dallas in 1952, Dr. Paul T. DeCamp and Associates read "A Paper on Suture Constriction of the Lung and Partial Thoracoplasty."[1] More recently[2] they have reviewed their four year experience with this procedure.

This paper describes our experience with the operation at Tranquille Sanatorium over an 18 month period, during which it was performed on 35 patients. The procedure was devised by Dr. Fernando Paulino, Rio de Janeiro.[3, 4]

The operation consists of removal of the second, third and fourth ribs in decreasing lengths from above downwards, followed by complete apicolysis (Fig. 1). The liberated apex of the lung containing the disease is then constricted by a series (usually three) of purse string sutures placed round it from above downwards. The apex is held in a curved clamp during the insertion of the sutures of No. 4 black silk or No. 10 crochet cotton. It is essential that the sutures should pass through both parietal and visceral pleura in order to prevent the lung from slipping downwards should a free pleural space exist. The extra-periosteal pneumolysis is carried to below the level of the diseased area; this may be to the level of the hilum on the mediastinal aspect and as low as the seventh interspace postero-laterally. Where the disease extends downwards, possibly into the superior segment of the lower lobe, we remove in addition, the posterior half of the fifth rib. In only one case has this resulted in a slipping scapula.

We favour the Paulino thoracoplasty because it is the procedure which fulfills most completely the requirements of the ideal collapse operation. These may be listed as follows:

1. The operation is applicable to cases of far advanced and bilateral tuberculosis.
2. There is only one stage.
3. No foreign material is introduced.
4. There is minimal deformity. The scapula remains outside the ribs.
5. There is maximum preservation of function.
6. The operation is safe. There are few post-operative complications.

In short, the operation gives permanent, selective, concentric collapse without the use of plombage material and without collapsing the disease onto mobile, elastic, active lung.

The following history (Case 1) is that of our first patient subjected to the operation.

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Presented at the Annual Meeting, Pacific Northwest Chapter, American College of Chest Physicians, November 12, 1954, Portland, Oregon.

Case 1: This 42 year old white prostitute was admitted with bilateral far advanced disease. After 13 months of antibiotic treatment, there remained diffuse infiltration and a 3 cm. cavity on the right side and a 1.5 cm. solid lesion on the left (Figs. 2 and 3.). A right Paulino thoracoplasty was performed, the first four and one-half ribs being removed (after the first five cases the first rib was left *in situ*). The early (Fig. 4) and ninth month (Fig. 5) post-operative x-ray film appearances are shown. Sputum conversion has been maintained now for two years. It is not known if she has returned to full time work. She refuses surgery for the left side.

Material.

Since May 1953 we have applied the procedure 35 times with gratifying results in 33 cases. The series includes 15 women and 20 men. Ages range from 21 to 59 years.

Extent of Disease.

	Per Cent
Far advanced	25.6
Moderately advanced	54.4
Minimal	20.0
Bilateral	51.4
Unilateral	48.6

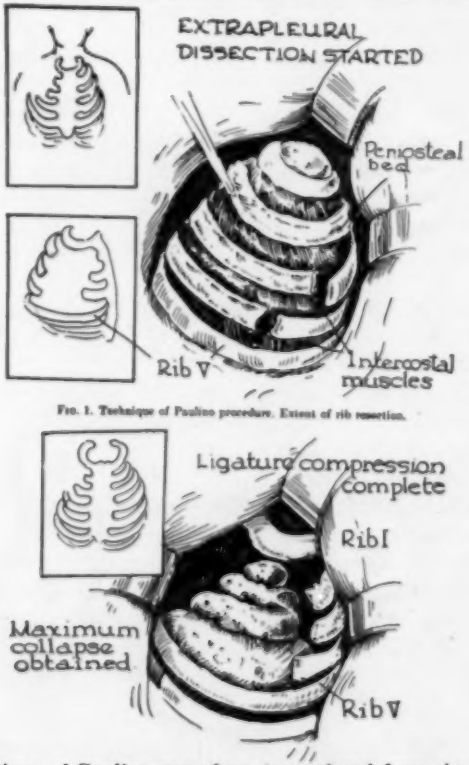

FIG. 1. Technique of Paulino procedure. Extent of rib resection.

FIGURE 1: Technique of Paulino procedure (reproduced from *Am. Review of Tuberculosis*, July, 1954, by permission of Editor and authors of "Suture Ligation of Lung and Partial Thoracoplasty").

Chemotherapy.

Almost all the patients had streptomycin and para-aminosalicylic acid, with or without isoniazid, for at least five months pre-operatively. Thus, many were already sputum negative on direct smear. In nearly every case antibiotics were discontinued two months post-operatively. The rationale being that tuberculosis heals by closure of the bronchocavitary junction and antibiotics would maintain the patency of the channels from the lesion to the exterior. In addition, the effectiveness of the collapse can only be assessed early in this way. This opinion is firmly subscribed to by Dr. Norman Wilson,[5] who discontinues antibiotics as early as one week following a plombage thoracoplasty. The exception to this rule occurs when there is potentially active contralateral disease which has not been sufficiently controlled by antibiotics pre-operatively.

Results.

There has been no operative death in this series. One patient, a 38 year old half-breed woman, with far advanced bilateral disease and cavities in all five lobes, died one month post-operatively from exacerbation of the disease. The only other major complication occurred when a 54 year old, frail Chinese male developed contralateral spread and later broncho extrapleural fistula. He is responding to drainage and further chemotherapy. The remaining 33 are well; 26 of them are at home, sputum negative on

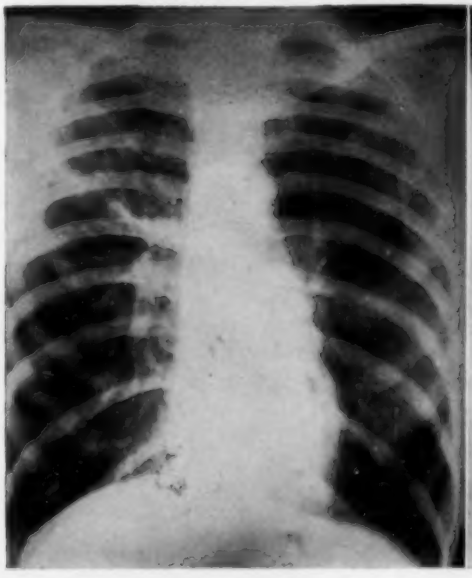

FIGURE 2

FIGURE 3

Figure 2—Case 1: Residual bilateral disease after 13 months of antibiotics. Planograms in Figure 3 show extensive right apical disease. *Figure 3—Case 1:* Bilateral planograms, showing the cavitated infiltration at the right apex which was collapsed and the small solid lesion on left side which the patient declined to have resected.

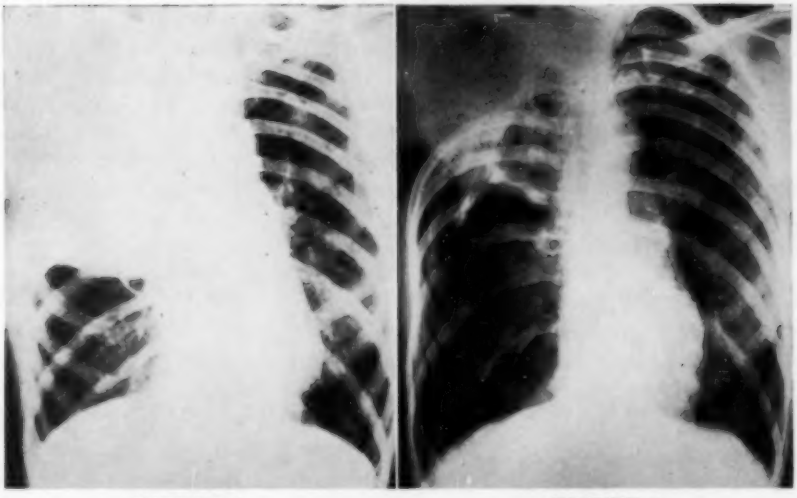

FIGURE 4 FIGURE 5

Figure 4—Case 1: Appearance 12 days following right Paulino thoracoplasty, ribs 1-5.
Figure 5—Case 1: Appearance nine months following right Paulino thoracoplasty.

culture six months upwards post-operatively. Of the eight now convalescing two have had additional surgery for contralateral disease, one a resection, the other a second Paulino thoracoplasty. Two are still sputum positive on smear. One requires resection of the collapsed disease. The other has the fistula referred to above.

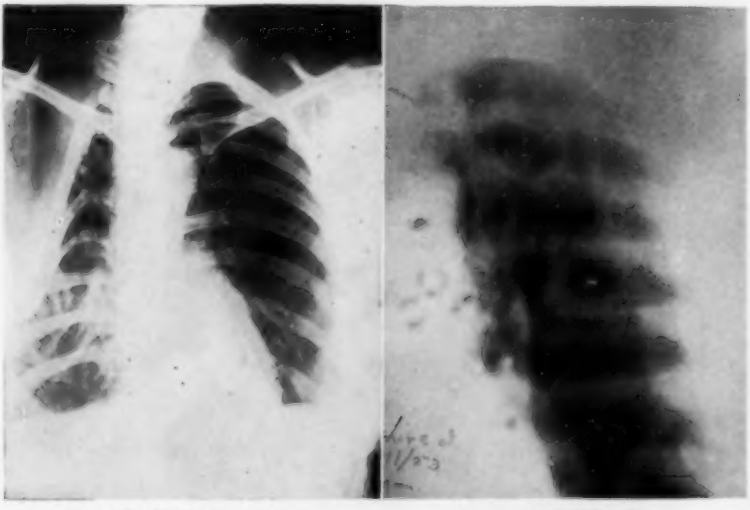

FIGURE 6 FIGURE 7

Figure 6—Case 2: Right thoracoplasty (four stages) fifteen years, new cavitated disease behind inner end left clavicle. *Figure 7—Case 2:* Left apical planogram showing cavity.

Complications.

1. Excessive extra-pleural fluid		1
2. Intra-pleural fluid		
without tear	2)	
with tear	2)	4
3. Infection of extra-periosteal space plus fistula		1
4. Exacerbation of tuberculosis (& death)		1
5. Contralateral spread of disease (same case as 3)		1
6. Slipping scapula		1
7. Phrenic nerve damage		1

In summary, nine patients had complications:

(a) Major: two cases, one death, one spread and fistula

(b) Minor: seven cases

The excessive extra-periosteal fluid was removed in one because of dyspnoea. There was an extensive contralateral thoracoplasty and pulmonary function was impaired. This compares favourably with the regime in plombage thoracoplasty. At the Overholt Clinic such aspiration is routine, at least once.

Case 2: This 39 year old white housewife had a four-stage right thoracoplasty 15 years prior to admission to our sanatorium in 1953. There was new cavitated disease at the left apex (Figs. 6 and 7). After 12 months of antibiotics a left Paulino thoracoplasty was performed. Portions of the second, third, fourth and fifth ribs were removed. Fluid was aspirated once from the left extra-periosteal space to relieve dyspnoea.

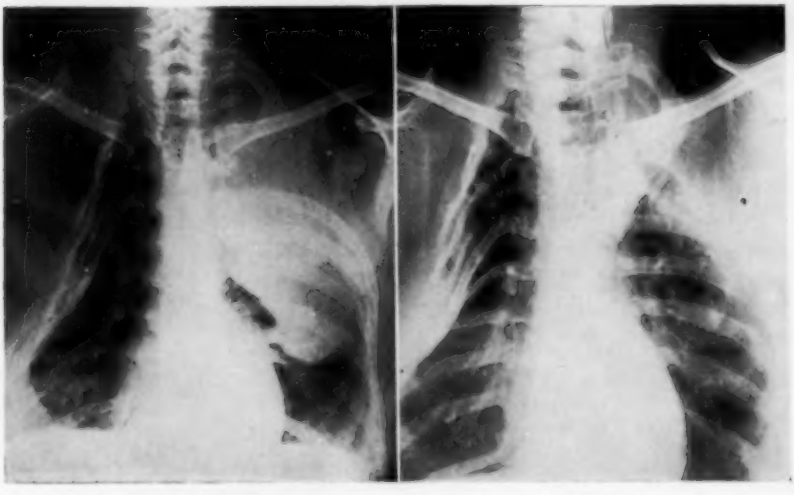

FIGURE 8 FIGURE 9

Figure 8—Case 2: Appearance eleven days following left Paulino thoracoplasty, ribs 2-5. *Figure 9—Case 2:* Appearance six months following Paulino thoracoplasty.

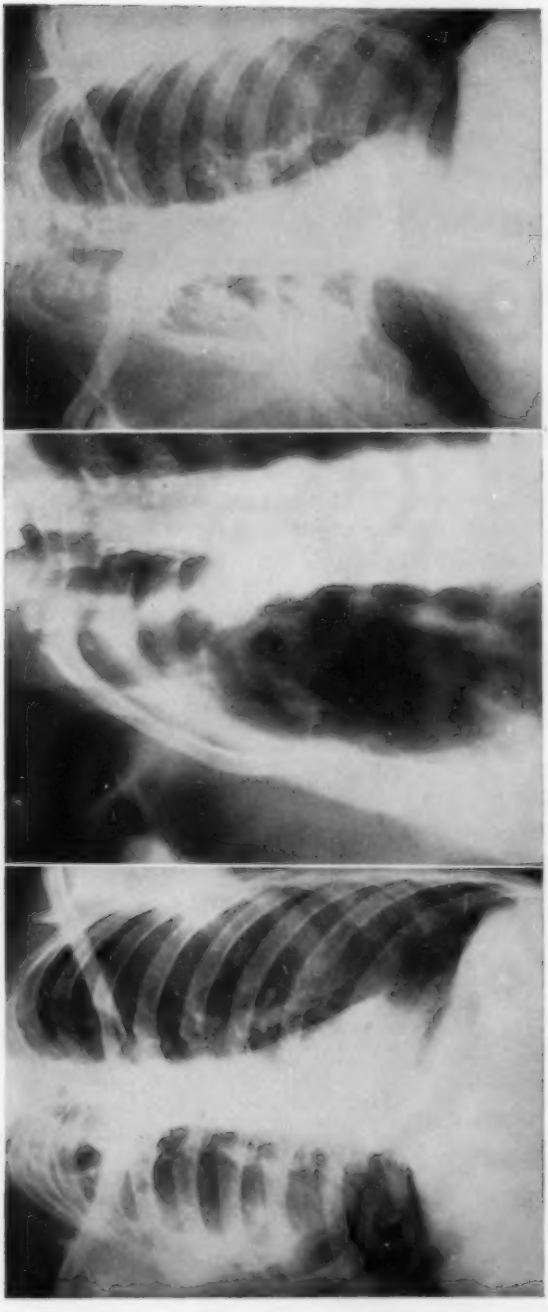

FIGURE 10

FIGURE 11

FIGURE 12

Figure 10—Case 3: Preoperative film. Former bilateral pneumothorax. Cavity right apex. *Figure 11—Case 3:* Right apical planogram showing 3 cm. cavity and thickened pleura. *Figure 12—Case 3:* Appearance one year following right Paulino thoracoplasty, ribs 2-6.

The 11th day post-operative x-ray film showed still a large extra-periosteal collection of fluid (Fig. 8) but after six months (Fig. 9) a satisfactory collapse was maintained. The maximum breathing capacity, meanwhile was 62.8 litres per minute, having been 75.7 litres per minute, pre-operatively. She is well and doing part-time work one year following surgery.

Intrapleural fluid developed in two cases without pleural tear having been noted. We believe with Dr. Wilson[6] that this is due to irritation by, or pressure from the extra-periosteal fluid through the thin anterior pleura.

Paroxysmal respiration has not been a troublesome feature in this series.

Case 3: A 37 year old white logger was presented for surgery with a five year history of pulmonary tuberculosis. Bilateral pneumothorax had been given for two years and discontinued for three years. A large cavity remained at the right apex, under a thickened pleura following hydro-pneumothorax (Figs. 10 and 11). Resection was the preferred treatment here. At operation a dense pleura, 1 cm. thick, was encountered over the whole of the lateral surface of the lung. To have done lobectomy would have required a long tedious operation with complete decortication of the lung. There was quite a strong possibility that pneumonectomy might be necessary. It was decided that a Paulino thoracoplasty was worth a trial. Soft pleura was encountered on the mediastinal surface and in spite of the thickness elsewhere, the apex was satisfactorily collapsed. Sputum conversion was quickly obtained. Because of the original intention to perform lobectomy this patient was operated upon in the face down position. No difficulty of access was encountered. He was back at heavy work one year post-operatively, and remains well six months later. Fig. 12 shows the final situation. The additional ribs were removed in connection with the planned resection.

Indications.

These are:

(a) *General,* where from a study of the course of the disease it is decided that some form of surgical assistance is necessary.

(b) Special, in which the thorny problem of collapse versus resection is raised.

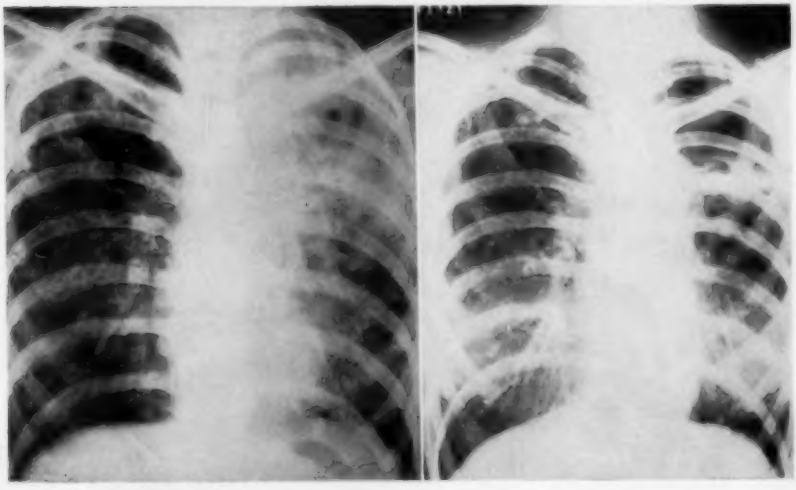

FIGURE 13 FIGURE 14

Figure 13—Case 4: Appearance at time of first admission to hospital. *Figure 14—Case 4:* After 23 months antibiotic therapy, a giant cavity remains in left apex, and a moderate amount of disease in the right.

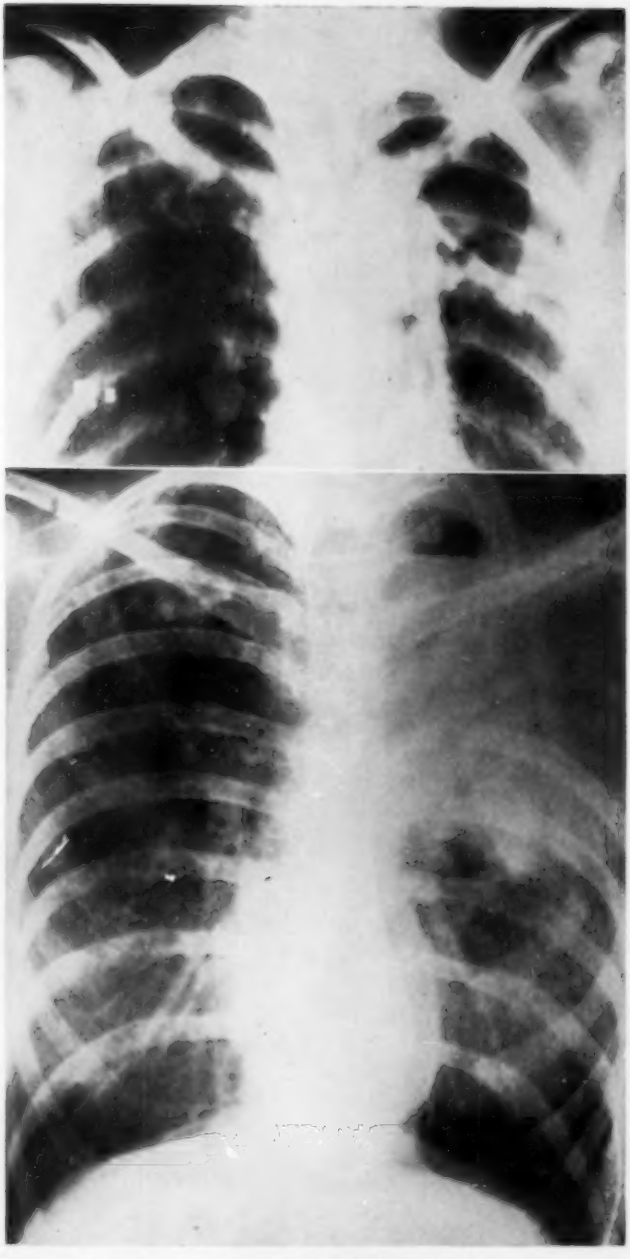

FIGURE 16

FIGURE 15

Figure 15—Case 4: Planegram, showing bilateral cavitated disease.
Figure 16—Case 4: Five weeks following left Paulino thoracoplasty, ribs 2-5.

Generally speaking, the operation was reserved initially for cases unsuitable for resection.

Case 4: This 25 year old white female, an alcoholic and borderline prostitute, was first diagnosed in 1948 with a minimal left upper lobe lesion. She did not attend for follow-up x-ray films until 1952 when far advanced bilateral disease was present (Fig. 13). She stayed in hospital for 11 months' antibiotic treatment, then signed out for five months. After 12 months' further antibiotic administration (Figs. 14 and 15) it was decided to attempt closure of the giant cavity in the left apex. Four-rib Paulino thoracoplasty was performed, and in spite of the low maximum breathing capacity of 39 litres/minute, was well tolerated. Five weeks post-operatively (Fig. 16) the amount of collapse appeared satisfactory. Eight weeks post-operatively she signed out again. She had been sputum negative on smear for about nine months at this time.

The indications are widening as results continue to give satisfaction. Now the operation is always considered where no solid lesion is present. It is a safer and much shorter procedure than resection. The factors of age, marginal respiratory reserve and general debility, favour its selection. Where resection of a lobe with a space reducing thoracoplasty is envisaged, many patients prefer to try the thoracoplasty first, especially when so hopeful an outcome can be promised at the expense of such a minimal removal of ribs. So far it has not been necessary to resect under a Paulino thoracoplasty. Doctors DeCamp and Acree do not mention this necessity either in their review of 42 similar operations, but Dr. Acree[7] has described to me two cases of resection which he has done subsequently. He encountered no difficulty whatsoever from the constricting sutures.

It is evident that this operation has a definite place in the armamentarium of the thoracic surgeon. As a prophylactic it is much less radical than resection of the residual, when the residual is not a clear cut, solid lesion. Indications for the Paulino thoracoplasty may well further widen as does our experience with the procedure.

Acknowledgments: It is a pleasure to record the excellent co-operation of the medical and nursing staff of Tranquille Sanatorium. The low incidence of post-operative complications is also a tribute to our anaesthetist, Dr. I. G. Smillie of the Burris Clinic, Kamloops, who gave all the anaesthetics. I am also indebted to the Division of Tuberculosis Control of British Columbia for assistance in the preparation of this paper.

Addendum: At the date of publication, one further patient (the one with spread and broncho-pleural fistula) has died. The two sputum positive patients have had their disease resected without difficulty.

SUMMARY

1. Experience of suture constriction of the lung with partial thoracoplasty (Paulino Procedure) in 35 cases is described.

2. This one stage operation gives permanent, selective, concentric collapse with minimal costal resection, and without the introduction of foreign (plombage) material.

3. The operation is safe with few post-operative complications and causes little function loss.

4. It is applicable to cases of far advanced and bilateral tuberculosis.

5. Six months after the last operation, 31 patients are well and sputum negative on culture, three have positive sputum (two of these require resection); one has died.

RESUMEN

1. Se describe la experiencia con la sutura constrictiva del pulmón combinada con toracoplastía parcial (procedimiento de Paulino) en 35 casos.

2. Esta operación en un tiempo, da un colapso concéntrico, permanente selectivo con un mínimo de resección costal y sin la introducción de plombaje de cuerpo extraño.

3. La operación es segura con pocas complicaciones postoperatorias y causa pequeña pérdida de función.

4. Es aplicable a casos de tuberculosis muy avanzada y bilateral.

5. Seis meses después de la última operación 31 enfermos estánbien y con esputos negativos al cultivo; tres tienen esputos positivos (dos de estos requiren resección); uno ha muerto.

RESUME

1. L'auteur décrit la suture constrictive du poumon associée à une thoracoplastie partielle (méthode Paulino) qu'il a pratiquée dans 35 cas.

2. Ce premier temps d'opération donne un collapsus concentrique permanent, électif, avec un minimum de résection costale, et sans l'introduction de corps étrangers (plombage).

3. L'opération est sans danger, occasionne peu de complications postopératoires et ne cause qu'un léger déficit de la fonction pulmonaire.

4. Elle convient aux cas de tuberculose avancée et bilatérale.

5. Six mois après le dernier temps opératoire, 31 malades étaient en bon état, avaient des crachats négatifs à la culture; trois avaient des crachats positifs, deux d'entre eux durent subir une résection. L'un mourut.

ZUSAMMENFASSUNG

1. Beschreibung der Erfahrung mit Einengung der Lunge durch Naht und mit Teilplastik (Vorgehen nach Paulino) in 35 Fällen.

2. Diese einzeitige Operation ergibt einen dauernden, selektiven und konzentrischen Kollaps mit minimaler Rippenresektion und ohne Einführung von Fremdkörpern (Plombierung).

3. Die Operation ist zuverlässig und mit wenig postoperativen Komplikationen verbunden und verursacht geringen Funktionsverlust.

4. Sie lässt sich anwenden bei Fällen weit fortgeschrittener und beidseitiger Tuberkulose.

5. 6 Monate nach der letzten Operation waren 31 Kranke wohlauf und im Sputum kulturell negativ; 3 haben ein positives Sputum (2 von diesen benötigen eine Resektion); 1 ist verstorben.

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Alveolar Cell Carcinoma

Review of the Literature, Clinico-Pathological Considerations, and Report of Two Cases†

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Introduction

In spite of the increasing frequency of recent case reports on alveolar cell carcinoma, this disease remains a diagnostic problem for experienced chest physicians, due to the paucity of symptoms. Neubuerger and Geever 1942 collected reports of 25 pathologically proved cases of alveolar cell carcinoma. The nomenclature of this disease is still an unsettled problem. Various authors have used different terms for what is conceivably the same pathological entity. Terms such as "adenoma-like tumor," "pulmonary adenomatosis," "primary multiple alveolar cell tumor," "papillary gelatinous adenocarcinoma," "alveolar cell carcinoma," "carcinosis," "diffuse epithelial hyperplasia," "alveolar cell tumor," "malignant adenomatosis," "muco-cellular papillary adenocarcinoma," "diffuse primary alveolar epithelial carcinoma," and "carcinomatoides alveogenica multicentrica" have been used to describe this disease. Recently, the terms most commonly employed are "pulmonary adenomatosis," "alveolar cell tumor," and "alveolar cell carcinoma."

Discussion

This disease was first described by Mallassez in 1876, and his case is considered a classical example of the multiple nodular form. In 1903, Musser reported another form of this disease as the diffuse variant. The occurrence of these two forms seems to be generally recognized and accepted.

The incidence of alveolar cell carcinoma varies from 3 to 5 per cent of all types of pulmonary carcinoma; however, with the rapidly increasing number of case reports, this percentage might not represent the true ratio.

It is as frequently encountered in women as in men. Neubuerger and Geever report the occurrence in 11 females and 12 males, and two of their cases give no notation as to sex. Watson and Davis found in a series of 33 cases, eight women and 25 men. Swan reported nine cases, eight of which were men; however, the high incidence of males is explained by the fact that they were selected from the Armed Forces Institute of Pathology.

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Goode and Cladgett's series contained seven women and five men. Davis and Simon's, Ikeda's, and the two cases in this paper are females.

It would appear from the data collected, that this disease affects persons of the older age group, predominately after the fourth decade of life.

Etiology

Various physical and chemical irritants have been considered as potential etiological factors. Grady and Stewart induced multiple alveolar cell tumors in the alveolar wall of mice by subcutaneous injection of dibenzanthracene. A case of bilateral alveolar cell carcinoma associated with the use of thorotrast was recently reported by Abrahamson et al. The authors describe the case of a female patient who died with alveolar cell carcinoma. She had been injected 16 years prior to her death with thorotrast, a radioactive material. They were able to demonstrate thorium in the spleen and liver, at postmortem. It was their opinion that the thorotrast in the body caused the alveolar cell carcinoma.

The possibility of viral origin has been strongly considered; however, substantiating evidence is lacking. Cowdry, et al were of the opinion that a disease known as "jaagziekte," which occurs in sheep and produces adenomatous lesions in the lungs of the animal is caused by a virus. Dungal, et al and Wood et al failed to transmit the disease by injecting rabbits, guinea pigs, and monkeys with human material. Chronic irritation, tissue susceptibility, and heredity have also been considered as possible factors.

Histogenesis

There is still considerable controversy concerning the possible alveolar origin of this tumor. Many authors believe it arises from the epithelium

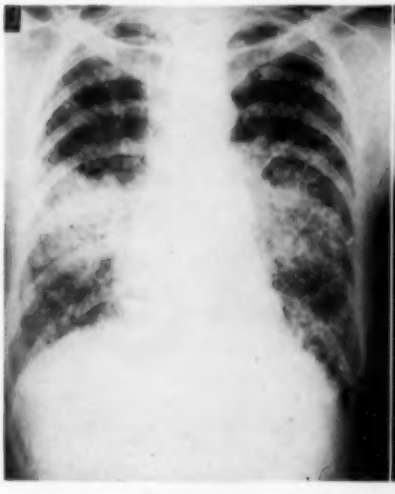

FIGURE 1

FIGURE 2

of the bronchi or terminal bronchioli. The presence of lining cells in the alveoli is still much debated. At present, three theories concerning the lining of the alveolus prevail:

(1) Maximow and Bloom, Lang, Fried, Loosi and others believe there is no epithelial lining of the alveoli after birth;

(2) Miller, Bremer, Cooper and others think there is a continuous epithelial lining;

(3) That there is a discontinuous lining with isolated cells of epithelial origin (Aschoff, Borgmann, and Seeman), or of entodermal epithelial origin (Clara and Macklin).

Geever, Neubuerger and Davis think that this isolated cell is of mesenchymal origin, identical with the so-called "septal cell" of Lang. This septal cell may, under various influences, become the origin of the alveolar cell carcinoma. The multicentricity of this tumor, which is one of the most characteristic pathological features, is explained on this basis. The lymphatic or vascular spread of the tumor, though possible, is unlikely. A recent theory expressed by Hutchison is that the growth may metastasize via air passages.

Case 1: E. E., a 68 year old white female, was admitted to the Missouri State Sanatorium on July 27, 1952. Family history was negative for tuberculosis. Past history revealed typhoid fever at the age of five, but no other history of disease was obtained. She stated that her health was good until March, 1952, when she noted slight dyspnea on exertion, non-productive cough, and the sensation of heaviness in her chest. These symptoms increased slowly and steadily.

In June, 1952, she was seen by a local physician, and treated symptomatically without relief. On July 7, 1952, she had a chest x-ray film, and the attending physician advised her to enter the Sanatorium for diagnosis and treatment.

On admission she complained of severe shortness of breath, a feeling of heaviness in the chest, dry hacking cough, and attacks of palpitation. Shortly before admission she had blood-streaked sputum on two occasions. Further questioning revealed that she had cleaned a chicken house in the spring, and she recalled that the dust caused severe coughing spells which persisted for seven to 10 days.

Physical examination revealed dyspnea but good nutrition. Pulse was 100-130; temperature, 98.6°, with slight evening elevation; respiration, 20-36; all other phases of the examination were negative except the liver was slightly enlarged, but not tender and the chest which revealed slight decrease resonance to percussion, bronchial breathing on auscultation, and marked wheezing over both lung fields.

Sputum smears and cultures were negative for tubercle bacillus. First and second strength tuberculin tests were negative as well as tests for blastomycosis and coccidioidomycosis. Histoplasmin reaction was 3+. All blood and urine examinations were essentially negative.

For the first two weeks following admission, her general condition remained almost unchanged, with the exception of steadily increasing dyspnea. X-ray film made on July 28, 1952 (Figure 1), showed many areas of nodular infiltration scattered uniformly throughout the whole right lung with a tendency of confluency in the right middle lung field. The left lung presented a similar reaction although the midlung field showed less confluency than that of the right. Subsequent films made on August 11, 1952 (Figure 2), and August 27, 1952 (Figure 3), showed progressive increase in disease in both lungs. On August 25, 1952, she began to vomit and complain of rapidly increasing weakness. Nasal oxygen and parenteral aminophyllin were administered without relief of dyspnea. Her general condition deteriorated rapidly and she expired August 31, 1952.

Pathological findings: The pleural cavities each contained 500 cc. of thin, pinkish-yellow fluid. The parietal pleurae were smooth and shiny, as was the pericardial sac. The mediastinal contents were not remarkable,

but the hilar lymph nodes were slightly enlarged, prominent, and contained gray tumor tissue. The heart weighed 332 grams, and was entirely within normal limits.

The lungs were grossly identical, the right weighed 823 grams, and the left, 773 grams. The visceral pleurae were smooth and glistening, but were noted to contain numerous raised, granular nodules of pinkish-gray, firm nature. These nodular areas measured from 1 to 3 mm. in diameter, and were also found in the interlobar regions. The lungs were firm and meaty to palpation, and the overall hue was that of a pinkish-black mottled surface. Multiple sectioning of both lungs revealed the entire pinkish-gray parenchyma to be diffusely studded with slightly elevated, discrete, gray tumor nodules, measuring up to 3 mm. in diameter. Careful dissection of the bronchi failed to show evidence of primary neoplastic growth. The vascular tree did contain several firm, small thrombo-emboli in its lesser peripheral radicles.

No evidence of primary malignant tumor was found anywhere in the body. The stomach, in the region of the cardia, contained five superficial ulcerated areas filled with blood. They were irregular in shape, and the margins were soft. The largest ulcer was 1.5 cm. in diameter, and no penetration of the serosa or muscular layers had occurred. The liver, spleen, pancreas, adrenals, abdominal lymph nodes, kidneys, uterus, and adnexa, and the balance of the gastro-intestinal tract were normal.

The microscopic alterations of the viscera were limited to the lungs, hilar lymph nodes, and stomach. All sections of the lungs revealed an overall miliary nodular transformation of the alveolar structure, with areas of normal alveolar framework. In the nodular areas, the alveolar skeleton was lined by a single layer of columnar epithelial cells which had

FIGURE 3

FIGURE 4

proliferated into papillary projections (Figure 5). These epithelial cells were neoplastic and possessed malignant features which consisted of loss of polarity of the hyperchromatic and slightly pleomorphic nuclei of these cells (Figure 6). There was, however, no distinct invasion of the broadened and fibrous alveolar septa. The adjacent alveoli were moderately collapsed. The bronchi and bronchioles were everywhere normal. Several of the smaller pulmonary arteries contained organized thrombo-emboli which almost completely occluded their lumens. None of these thrombi contained tumor cells. The hilar lymph nodes showed a partial replacement of normal architecture by papillary neoplastic tissue identical with that noted in the lungs. The gastric ulcerated sites were void of mucosal and submucosal layers, while a moderate infiltration of acute and chronic inflammatory cells had occurred in the muscular and serosal coats. In the mid portions of the ulcers several small arteries were noted to be completely occluded by organized thrombo-emboli. No evidence of malignancy was found.

The final anatomical diagnosis was alveolar cell carcinoma of lungs, with metastasis to hilar lymph nodes, thrombo-emboli of lungs and stomach, acute ulcerations of stomach, terminal (?), and atelectasis of lungs, focal.

Comment on Case 1

Symptomatology consisted of rapidly increasing dyspnea, dry cough, and absence of anemia, or any appreciable weight loss. The clinical findings of negative sputa, negative skin tests, and lack of general toxicity were in marked discrepancy with the x-ray findings, and made the diagnosis of miliary tuberculosis very doubtful. The possibility of berylliosis was eliminated by negative history of exposure. Histoplasmosis was considered a likely diagnosis because of a history of exposure to dust in a chicken house, and also showed a 3+ histoplasmin skin reaction. There is a striking similarity between this case and the report on 24 soldiers diagnosed as a new medical entity called "Cave Disease." Furcolow later proved, however, that the etiology in these cases was Histoplasma capsulatum.

Further investigations revealed negative complement fixation for histoplasmosis, and negative fungi cultures. The diagnosis of histoplasmosis was then considered less likely. Metastatic carcinoma was also considered; however, no evidence of primary pulmonary carcinoma was found clinically. By exclusion we arrived at a clinical diagnosis of sarcoidosis or alveolar cell carcinoma. Three important diagnostic procedures lacking in this case were cervical lymph node biopsy, sputum examination for cancer cells, and lung biopsy.

Case 2: S. G., a 45 year old white female was admitted to Missouri State Sanatorium on May 12, 1952. Family history was negative for tuberculosis and carcinoma. She had hysterectomy and left oophorectomy for non-malignant tumor in October, 1945. From 1944 to 1945 she worked as a cook in a state institution, and had regular x-ray films which were interpreted as normal.

This illness began in November, 1951, with gradually increasing dyspnea, non-productive cough, undue fatigue, chest pain, and night sweats. Dyspnea increased rapidly, and she was forced to stop work in March, 1952. An x-ray film was taken and she was advised to enter the sanatorium for diagnosis and treatment.

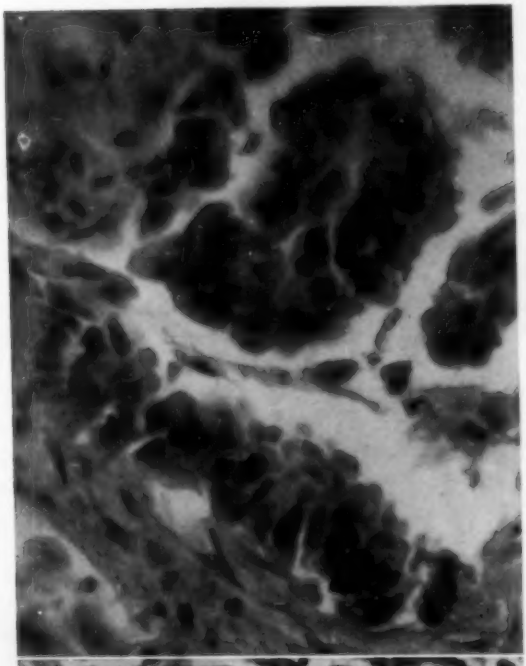

FIGURE 6

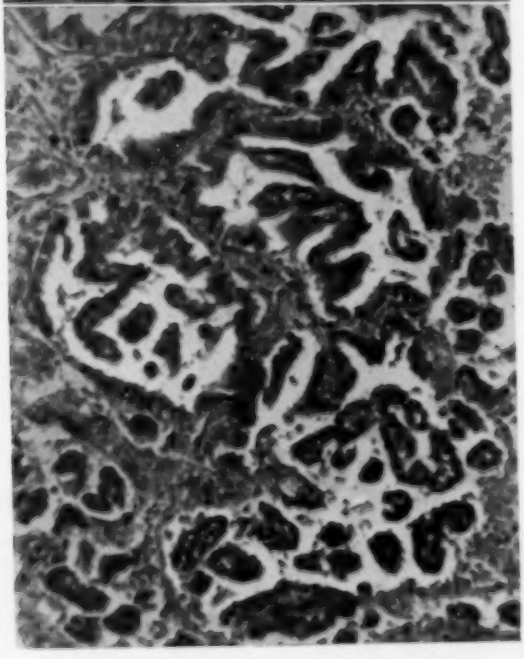

FIGURE 5

Figure 5: The alveolar tumor shows a papillary type growth (Case 1).
Figure 6: There is a loss of polarity of the nuclei with some piling (Case 1).

Physical examination revealed a weak, moderately dyspneic woman in good nutrition. Some dysphonia was present. Pulse ranged from 90-110; temperature was 98.6°; respiration 28; and blood pressure 118/78. Physical examination was noncontributory except the chest findings. There was dullness over the superior half of the right lung field and the left lung. Scattered rāles were elicited throughout both lungs. With the exception of a postoperative scar in the hypogastrium, the abdomen was normal.

A posterio-anterior x-ray film on May 13, 1952 (Figure 4), showed a dense homogeneous shadow in the right upper lung field, as far down as the fifth rib posteriorly. Below this, were scattered areas of multiple nodular infiltration. The left lung showed the same type of infiltration scattered throughout.

An electrocardiogram showed evidence of right heart strain. Sputum was negative for tubercle bacilli, both by smear and culture. First strength tuberculin skin test was +2. Histoplasmin test was negative, and coccidioidin test was +1. All phases of the blood and urine examinations were essentially normal but chest aspirated sediment was positive for malignancy.

On admission to the hospital she was placed on antibiotics but remained dyspneic and cyanotic, and showed no sign of improvement. On May 15, 1952, she had a convulsive seizure with carpo-pedal spasm which lasted 20 minutes. Blood chemistry analysis revealed CO_2 combining power of 82 vol. per cent. On May 17, 1952, she had a similar, but lighter, attack. Subsequent CO_2 determinations showed return to normal and no further seizures occurred. Following these episodes, she gradually deteriorated, went into coma on June 1, 1952, and died in respiratory failure. Permission for autopsy examination was denied, but needle biopsy of the lungs was done. The gross characteristics were those of several small, worm-like portions of pinkish-gray tissue, up to 12 mm. in length, and 2 mm. in diameter. These were examined microscopically. Histological examination revealed small remnants of normal-appearing pulmonary alveoli. The normal architecture of the lung structure was obscured by the presence of neoplastic papillary alterations (Figure 7). The alveolar framework was faintly perceptible and was noted to be lined by columnar epithelial cells. These cells were arranged in papillary formation, and showed loss of polarity of the nuclei. Mitotic figures were absent, but the cells and their nuclei were hyperchromatic and slightly pleomorphic (Figure 8). There was a pronounced fibrous tissue proliferation in the alveolar walls, with thickening of these walls. No area in the biopsy material could be found where it was definitely observed that invasion had occurred. There was the same overall macronodular pattern in this as in the first case, areas of alterations of normal uninvolved lung parenchyma with those of tumor nodularity.

Anatomical diagnosis: Compatible with alveolar cell tumor of lung.

Pathological Comment

In both cases, the usual and typical gross nodularity is apparent, both in the x-ray films and the sections. Even though a small portion of lung tissue was obtained by needle biopsy, there were normal areas of lung tissue with an overall pattern of nodularity of the malignant component. The same papillary arrangement was evident and the same alveolar lining was present in the second case. There appears to be a slightly higher degree of anaplasia of the tumor cells in Case 2, inasmuch as there is more distortion, which we feel is due to preparation of such a small specimen. Both cases are considered to be definite carcinoma, proved histologically, of the alveolar cell type. Both are papillary in nature, show fibrous proliferation intra-alveolarly, with no distinct evidence of glandular invasion of these thickened alveolar walls. Since Case 2 was not autopsied, there is the possibility that a primary tumor in the lung may have been present. Also, we do not know about hilar lymph node metastasis in this case. We do feel, however, that the histopathologic changes show sufficient criteria for a diagnosis compatible with alveolar cell carcinoma. These microscopic changes, along with the clinical and roentgenological findings are deemed of sufficient evidence to include this case in our paper. There is no doubt

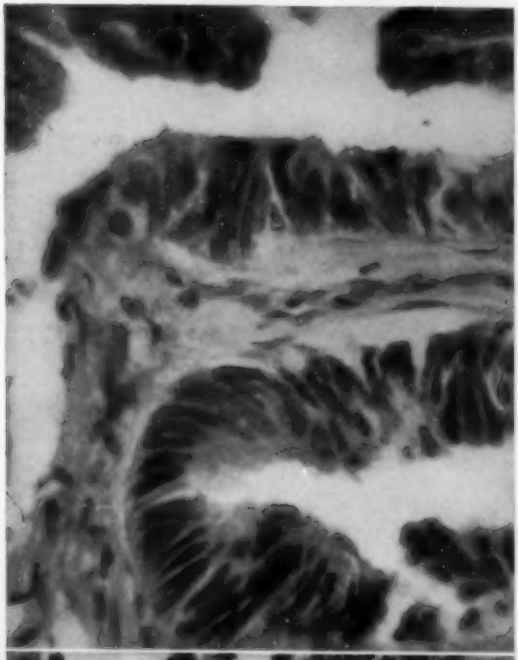

FIGURE 7

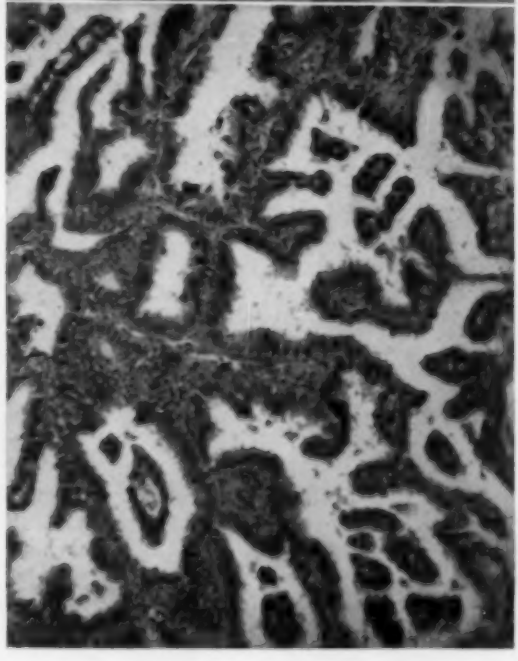

FIGURE 8

Figure 7: A typical alveolar arrangement is noted with papillarity (Case 2).
Figure 8: Note the hyperchromatism, pleomorphism and polarity disarrangement (Case 2).

in our minds of the true validity of Case 1 having the needed criteria for a perfect example of alveolar cell carcinoma.

Discussion

We will not attempt to further discuss the histogenesis of alveolar cell tumor. The recent medical literature has a multitude of papers attempting to identify the etiology of this disease. Bonne found the morphological resemblance of pulmonary adenomatosis (jaagziekte) in sheep to certain lung cancers in men, and discussed the possibility of a viral origin of the alveolar cell tumor.

It is of interest to note that Davis and Simon had a series of cases, all of which were women.

Concerning the duration of disease, little can be said, since there is a wide variation from a few weeks to several years, in cases published in the recent literature.

SUMMARY

1. Alveolar cell carcinoma has been discussed with reference to etiology, histogenesis and histopathology.

2. Two illustrative case reports with emphasis on differential diagnosis have been presented.

3. Presence of the columnar epithelial lining of the alveolar framework with papillary projections, loss of polarity of the hyperchromatic and pheomorphic nuclei of these cells, lack of invasion of alveolar septa and normal bronchioli favor the theory of an intrinsic low malignant alveolar tumor.

RESUMEN

1. El carcinoma de células alveolares se ha discutido haciendo referencia a su etiología, histogénesis e histopatología.

2. Dos casos ilustrativos se han presentado con énfasis en el diagnóstico diferencial.

3. La presencia de epitelio columnar rodeando pared alveolar con proyecciones papilares, la falta de polaridad de los núcleos hipercromáticos y pleomórficos de estas células, la falta de invasión del tabique alveolar y los bronquiolos normales favorecen la teoría de un tumor intrínseco alveolar de baja malignidad.

RESUME

1. Les auteurs mettent en discussion la notion de cancer alvéolaire en se basant sur l'étiologie, l'histogénèse et l'histopathologie.

2. Ils présentent deux observations illustrant leur communication et insistent sur le diagnostic différentiel.

3. La présence de couche épithéliale bordant la structure alvéolaire avec projections papillaires, la perte de la polarité des noyaux hyperchromatiques de ces cellules, l'absence d'envahissement des cloisons alvéolaires et des bronchioles normales sont en faveur de la théorie d'une tumeur alvéolaire maligne.

ZUSAMMENFASSUNG

1. Es wurde über das Alveolarzell-Karzinom unter besonderer Berücksichtigung der Ätiologie, Histogenese und Histopathologie berichtet.

2. Es wurden zwei charakteristische Fälle mitgeteilt, und deren Differentialdiagnose erörtert.

3. Das Vorhandensein von säulenförmigen Epithelwucherungen des Alveolarnetzes mit papillären Ausstülpungen, der Verlust der Polarität der hyperchromatischen und pleomorphen Nuclei dieser Zellen, der Mangel an infiltrierendem Wachstum in die alveolären Septen und normale Bronchioli begünstigen die Annahme des Vorliegens eines wenig malignen Alveolartumors.

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Pulmonary Amoebiasis

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Entamoeba histolytica reaches the lung through any of the following channels:

1) Direct continuity of tissue from a perforating liver abscess rupturing into the lung across the diaphragm. This is the commonest variety, and was described by Kartulis of Alexandria as early as 1886.

2) Through the diaphragmatic lymph channels from amoebic hepatitis or a distant liver abscess without direct continuity of necrosis. This is a less common form.

3) Through the systemic venous circulation. The infection is relayed from the portal tract by way of some of the anastomotic channels that exist between the systemic and portal circulations. Since the liver contains the vastest anastomotic net between the two systems, it probably acts as the relay station in the majority of instances, rather than the haemorrhoidal veins or the thoracic (chyle) duct. This form is rare and probably takes place only in association with a massive infection dose, for example: polluted water supply.

Once the entamoebae reach the lung parenchyma and histiolytic processes follow, it is theoretically possible that further spread into the lungs can occur along the bronchi from aspiration (in-coughing) of necrotic material.

Clinically lung amoebiasis is met under the following four varieties:

1) Lower lobe involvement with the diaphragm perforated.

2) Upper lobe involvement with an intact diaphragm.

3) Disseminated focal lung infiltrations.

4) Solitary abscess.

1—*Lower lobe involvement with the diaphragm perforated:*

This is due to a perforating abscess and is characterised by the usual signs and symptoms of liver abscess. In its early phase, there is a stage of hepatitis of varying intensity from the acute to the mild chronic. Lymphatics are capable of carrying the infection a long distance from the underlying focus of amoebic necrosis to and across the diaphragm.

Spread along the lymphatics, before the actual process of liquefaction that follows in its wake, is responsible for two phenomena:

a) Occurrence of an early stage of significant signs and symptoms due to irritation of the diaphragm expressed as pain, hiccup and reflex cough. The muscles of the abdominal wall may show some rigidity and resistance to palpation with diminished mobility.

b) A process of plastic pleuritis in an attempt to prevent rupture of the abscess inside the pleura, a rare occurrence in clinical practice.

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Diaphragmatic immobility in its early stages is best discerned by the fluoroscopic screen, but later such signs as lack of movement of the right rectus muscle or diminution in diaphragmatic excursion as determined by tidal percussion from the back are obvious. Cough is unproductive or may yield frothy white sputum and be accompanied by a pleural stitch. As the abscess encroaches on the lung, the diaphragm rises and compresses the lower lobe to a variable extent.

The diaphragmatic outline describes a significant hump in part of its length, while the costophrenic angle is narrowed and obliterated or hazy from pleural reaction. The lung shows the usual signs of consolidation and superadded exudate, and where deep bronchial breathing is heard best, this is the area nearest to the abscess.

The general appearance of the patient is constituted by muddy earthy colour with subicteric tint and dark pigmentation. If a large part of the liver is affected, generalised oedema of nutritional origin may be present, due to the fact that the liver is the main organ concerned with the production of serum proteins. The condition quickly subsides on treatment, correct diet, aided by blood transfusion. As the abscess gets near a large bronchus, haemoptysis is common.

One day, not long afterwards, the patient coughs up a large amount of dark chocolate coloured material, devoid of organisms, but may contain charcot-leyden crystals.

It may have a bitter taste, which is significant since it is unique in this property. By x-ray film the liver is seen to shrink in size sometimes considerably as seen by the receding edge and the deflated diaphragm, which by now has a characteristic shape, of everted edges and a central funnel with a hydroareal cavity below it.

Case 1 was a male aged 61 years who suffered for two and one-half months before admission from heaviness and tender swelling in the right hypochondrium, dyspnoea and cough which was later accompanied by expectoration of a moderate amount of brownish, bitter sputum. He gave a history of a single attack of diarrhoea, tenesmus and blood in stools few months before the present condition. He was pale and toxic,

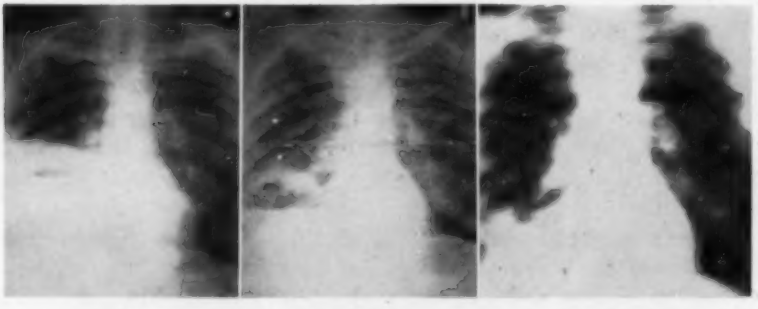

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1 (Case 1): Before treatment and after aspiration and air injection, showing high cupola of right diaphragm and hydroareal cavity in liver.—*Figure 2* (Case 1): Diaphragm lower in position. Hydroareal cavity still present.—*Figure 3* (Case 1): After treatment cavity completely disappeared, diaphragmatic regression and residual basal lung fibrosis. Symptom free 9 months later—December 9, 1954.

feverish with puffy eyes and soft pitting oedema in the lower limbs. There was dullness starting from the third right intercostal space. The lower border of the tender liver was felt four fingers below the costal margin. In the epigastrium there was a boggy cystic and fluctuant swelling. Fluoroscopy showed a high immobile diaphragm, the leucocytes were 22.000/cubic mm. with 94 per cent polymorphs, the blood sedimentation rate was 60/94 (Westergren). Stools were repeatedly negative for amoeba.

He received 10 grains of emetine in a daily dose of 1 grain, aureomycin 1 gm./day for 10 days and chloroquine 1x3 for 20 days. Three blood transfusions and one plasma transfusion 500 cc. each were given at intervals. Daily aspiration for five days and then every other day for another five times were performed and a thick dark brown material ranging from 600 cc. at the start to few cc. at the end were aspirated. Local instillation of ¼ grain emetine and 125 mgm. aureomycin were done after every aspiration for the first five aspirations.

From the third day the temperature was normal, and at the end of treatment all symptoms disappeared with regression of the liver swelling and complete disappearance of the cystic area in the epigastrium.

2—*Upper lobe involvement with an intact diaphragm:*

This is a much less common form than the preceding one. In this type the diaphragm is raised and of limited mobility but its contour is preserved. The upper lobe affection dominates the picture, while the lower lobe is significantly free except for a tell-tale leash of increased linear markings due to infiltrated lymphatics accompanying the main inferior bronchus and leading to the hilum.

The radiographic picture shows dense opacity of the upper lobe that undergoes cavitation if not recognised and treated early.

Case 2 was a male aged 45 years who had been admitted in 1939 complaining of dyspnoea, cough and expectoration for seven days. Signs of consolidation in right upper lobe were evident accompanied with fever ranging from 37.5 to 39 C. for two weeks that did not respond to sulphonamides. The rise in the cupola and the pain and tender one-finger-enlarged liver was considered significant and a course of emetine was started. The response was evident after 3 grains. The temperature dropped to normal, sputum and stools were negative for amoebae from the start

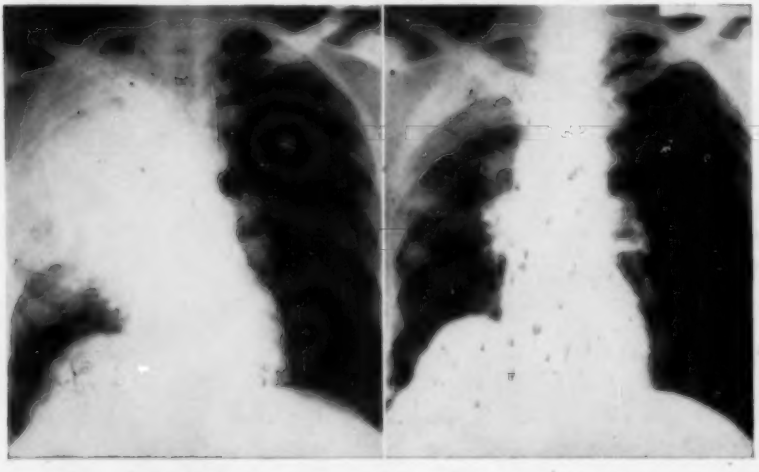

FIGURE 4 FIGURE 5

Figure 4 (Case 2): Consolidation of right upper lobe due to amoebic pneumonitis. Note the doming of the cupola of the diaphragm and leash of lymphatics from diaphragm to the hilum.—*Figure 5* (Case 2): Resolution after emetine treatment.

3—*Disseminated focal lung infiltrations:*

This variety is decidedly rare. It is represented by disseminated focal lung infiltrations, and is caused by blood borne dissemination, presumably from a primary massive infection dose as occurs from polluted water.

Such a mode of infection has also been reported by Keeton and Hood in the late Chicago epidemic where several hundred people were infected by polluted water.

Beyond the usual clinical signs of consolidation, the x-ray film shows wide-spread cotton-wool opacities scattered over both lung fields not unlike acute bronchopneumonic disease.

The liver though somewhat enlarged and tender is not the focus of primary attention and may even escape notice.

Repeated sputum examinations offer the best clue in this type when found positive for Entamoeba histolytica.

Case 3: A young adult Libyan prisoner of War about 25 years old was admitted to hospital in 1941 under the preliminary diagnosis of pulmonary tuberculosis. He had a dusky face and though he was badly nourished he did not look seriously ill.

He complained of moderate fever and pain in the right chest for 15 days. He coughed up blood-tinged sputum which resembled currant jelly in appearance and was sticky. There was a previous history of dysentery in Tobruk some few months before, for which he received a few pills. The amount of sputum was about 60 cc. daily, which had neither odour nor taste. The chest signs were those of wide-spread consolidation in both lungs with some exudate. There was pain all along the liver margin, but this organ was not appreciably enlarged. The x-ray film showed scattered cotton-wool patches in both lung fields not unlike acute broncho-pneumonic tuberculosis, but nodular mottling, characteristic of the latter disease, was absent. There was, however, one thing obvious; the severity of the lesions on the x-ray film did not carry with it a corresponding serious or a grave clinical appearance; and it became increasingly evident that we were dealing with an unfamiliar type of infection. His sputum was repeatedly examined for tubercle bacilli, spirochaetes, fungi, monilia and amoeba. At first only ordinary microbic flora were reported, but on the third examination entamoeba was discovered. Treatment with emetine was speedily successful. From the third injection his sputum cleared of blood and his chest from the pain, and the fever disappeared in a few days. He took two courses of emetine, one of 12 grains, followed by two weeks rest and then 8 grains for his chest to be radiographically clear.

4—*Solitary abscess:*

This is usually but not invariably in the right lung, being often situated in the apex of its upper or lower lobes, the liver and diaphragmatic

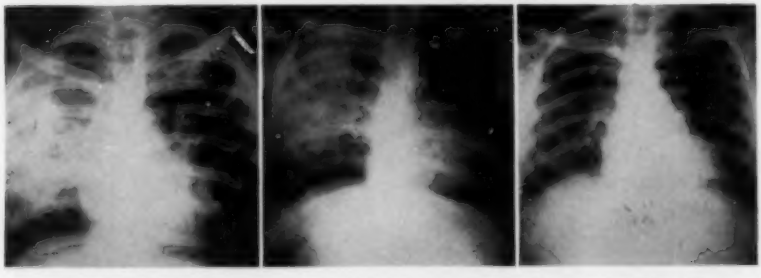

FIGURE 6 FIGURE 7 FIGURE 8

Figures 6, 7, 8 (Case 4): The Libyan prisoner described in the text. The sputum contained Entamoeba histolytica. The x-ray is indistinguishable from the acute "cotton wool" patches of pulmonary tuberculosis. Two courses of emetine were necessary to effect complete cure. There were no appreciable liver signs. Cases observed during the war.

affection is outstandingly minimal or absent. To distinguish this abscess from other varieties of lung abscess is difficult especially if it is not preceded or accompanied by active amoebic dysentery.

Sputum examination often offers no help, but the dramatic response to emetine is significant but carries with it the time honoured criticism "Post Hoc Ergo Propter Hoc," a dangerous dictum but in this group of cases at least, owing to lack of something better to go by, we are obliged to accept. A useful point of differentiation is that the patient in the early stages is as a rule not so markedly ill as in the acute abscess of the microbic aetiology; unless the abscess is superimposed on a previous debilitating disease such as chronic diarrhoea, malnutrition or diabetes.

Case 4 was admitted in 1939 with cough, foul sputum with blood. Improvement occurred on benzoate therapy and N.A.B. (a treatment that was in common practice at that time). Odor and sputum were completely abolished since the first injection of emetine 1 grain. Twelve injections of emetine were administered with complete symptomatic recovery. It is noteworthy that there is no previous history of dysentery in this case.

Until a few years ago emetine was the sovereign remedy.

In recent years we have found that a combination of terramycin in 1.5 gm./day dose combined with daily chloroquine 0.75 gms. and emetine one grain for six to eight days eminently successful in establishing rapid improvement hitherto unequalled. Blood transfusions are indicated to correct the hypoalbuminaemia attendant to the first group of cases of liver hepatitis and abscess formation. Terramycin overcomes the secondary invasion while chloroquine maintains the antimamoebic activity and both are continued for 10 to 15 days after emetine is stopped. Intravenous calcium therapy has been found useful to raise the blood pressure, which may drop unduly under emetine, when coramine, ephedrine, or strychnine have not been found successful.

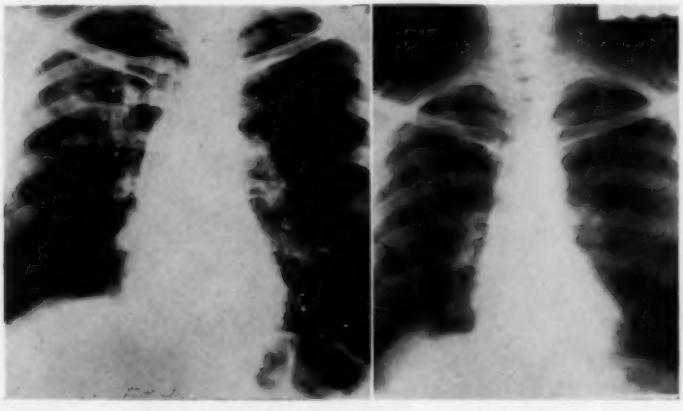

FIGURE 9 FIGURE 10

Figure 9 (Case 4): Solitary lung abscess in right upper lobe. Note the raised diaphragm and the tell-tale leash of the affected lymphatics spreading from the hilum.—*Figure 10* (Case 4): Abscess closed with residual fibrosis after 12 grains of emetine.

SUMMARY

Clinically lung amoebiasis may be encountered in the following forms:

1. From perforation of an associated liver abscess across the diaphragmatic barrier. This is the most common variety.

2. From lymphatic spread across the diaphragm in which this organ remains intact, albeit raised and immobile. There is consolidation and possible consequent necrosis of lung tissue in the lobes of the right side.

3. From systematic venous dissemination causing wide-spread "cotton wool" patches of bronchopneumonia and scattered over both lung fields. The condition is probably associated with massive infection dose e.g. a polluted water supply.

4. The solitary abscess without other amoebic manifestations elsewhere in other organs. The therapeutic test provides the only questionable evidence for its etiology.

The combined treatment of aureomycin, emetine and chloroquine affords the speediest cure so far achieved in the treatment of lung and liver amoebiasis.

RESUMEN

Clínicamente la amibiasis pulmonar puede encontrarse en las formas siguientes:

1. Por la perforación de un absceso del hígado a través de la barrera diafragmática. Esta es la variedad más común.

2. Por diseminación linfática a través del diafragma cuando este órgano queda intacto aunque elevado e inmóvil. Hay consolidación y posible consecuente necrosis del tejido pulmonar en los lóbulos del lado derecho.

3. Por diseminación por la red venosa general causando amplia diseminación con aspecto de manches algodonosas, manchas de bronconeumonía, diseminadas en ambos pulmones. La condición está probablemente asociada con una dosis masiva de infección tal como ocurre con las aguas contaminadas.

4. El absceso solitario sin otras manifestaciones amibianas en otros órganos. La prueba terapéutica provee sólo una evidencia dudosa de la etiología.

El tratamiento combinado con aureomicina, emetina y cloroquina proporciona la curación más rápida hasta ahora alcanzada enel tratamiento de la amibiasis pulmonar y hepática.

RESUME

Cliniquement, l'amibiase pulmonaire peut être rencontrée dans les formes suivantes:

1. Après perforation à travers la coupole diaphragmatique d'un abcès du foie associé. C'est la forme la plus courante.

2. Après propagation lymphatique à travers le diaphragme, celuici demeurant intact, bien que surélevé et immobile. Il y a consolidation et par suite nécrose possible du tissu pulmonaire dans les lobes du côté droit.

3. Après propagation veineuse déterminant des taches largement étendues d'aspect cotonneux de bronchopneumonie, disséminées sur les deux champs pulmonaires. Cette éventualité est probablement en rapport avec une infection massive, par exemple par un apport d'eau polluée.

4. L'abcès isolé sans autres manifestations amibiennes des autres viscères. Le test thérapeutique est la seule preuve, d'ailleurs non absolue, de son étiologie.

La traitement combiné par l'auréomycine, l'émétine, et la chloroquine apporte la guérison la plus rapide et la plus efficace dans l'amibiase pulmonaire et hépatique.

ZUSAMMENFASSUNG

Klinisch kann man die Lungen-Amoebiasis in den folgenden Formen antreffen:

1. Von der Perforation eines begleitenden Leberabszesses aus durch die Zwerchfellschranke. Dies ist die häufigste Variante.

2. Von einer lymphogenen Aussaat durch das Zwerchfell, bei dem dieses Organ intakt bleibt, obgleich hochgestellt und unbeweglich. Es besteht eine Verdichtung und möglicherweise nachfolgende Nekrose von Lungengewebe in den Lappen der rechten Seite.

3. Von einer Aussaat durch das Vene-System, die zu einer weiten Ausbreitung von watteförmigen Flecken von über beide ganze Lungen verstreuten Bronchopneumonien führt. Diser Zustand ist wahrscheinlich verbunden mit einer massiven Infektionsdosis, das heisst einer verunreinigten Wasserversorgung.

4. Der solitäre Abszess ohne andere amoebiale Manifestationen in irgend welche andere Organe. Der therapeutische Test ermöglicht den einzigen unzweifelhaften Beweis seiner Aetiologie.

Die kombinierte Behandlung mit Aureomycin, Emetin und Chloroquin erlaubt die schnellste bisher erreichte Heilung bei der Behandlung der Amoebiasis von Lunge und Leber.

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Autonomic Changes in Chronically Ill Patients

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Preliminary Report

From witch doctor to 20th century specialist, every thoughful physician has been interested in the relationship between the patient's disease and his emotional equilibrium. This is particularly true of chronic illnesses.

To date, attempts to find meaningful relationships have been made chiefly by psychiatrists and psychologists, who have based their research on essentially subjective techniques. Neurophysiologists have examined every body fluid from blood to sweat, in an attempt to separate the mentally healthy from the mentally unhealthy, generally with indifferent success. Both psychiatric subjective examinations and objective physiologic ones require experienced examiners, research laboratories, or both, generally not available to the general practitioner or sanatorium physician.

Recently, Dr. Funkenstein and his associates[1-4] have extensively studied the reaction to two autonomic drugs, epinephrine (sympathetic) and Mecholyl (parasympathetic). Their subjects included patients with various psychosomatic disorders, mental patients, and healthy Harvard Medical College students. Physical reactions were measured by systolic blood pressure. Psychosomatic reactions included chills, anxiety attacks, and other physical symptoms, typical of the patient's usual reaction to stress.

It was found that patient reactions differed markedly from that of the student controls, especially in response to Mecholyl. Students' blood pressure after injection fell but returned to the control base level within the 25 minute test period. (Group 2-3) Patients' blood pressure either failed to return to basal level (Group 6), returned and overshot (Group 1 and 4) or a chill prevented accurate measurement of blood pressure (Group 7). (Figure 1).

In evaluating the test, Gellhorn[5] described Funkenstein's groups as "normal" Central Sympathetic Reactivity, C.S.R., (Group 2-3), increased C.S.R. (Groups 1 and 4), and decreased C.S.R. (Group 6). Group 7 would then constitute an "unknown C.S.R.," although in our experience with serial testing, these patients on subsequent tests usually showed decreased C.S.R. (Group 6) Gellhorn's classification is useful, since various psychiatric physical therapies alter the patient's response to such an extent that reactions cannot be placed accurately in Funkenstein's rigid grouping.

As an objective measure of psychophysiological balance, we have found the test a reliable guide to treatment of mental patients. As the sedimen-

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From the Owen Clinic.

[1]This study was supported by the O. C. Institute and the Beverly Hills Woman's Club, Huntington, West Virginia.

[2]From the Owen Clinic, Huntington, West Virginia.

tation rate reflects the activity of chronic infections, so does the Funkenstein test reflect the changing balance of the emotionally disturbed. In view of this fact, we felt it would be of interest to determine how reactions of patients with chronic diseases compare with that of the frankly mentally ill.

Method

Material: One hundred thirty-five persons have been examined 400 times. Of these, five groups of 12 patients each were selected and matched according to age and sex (Table I). Group A consisted of outpatient tuberculous patients receiving collapse therapy, anti-microbials or both. All were working full or part-time. Group B comprised those with various chronic disorders (rheumatoid arthritis, cerebral palsy, epilepsy, and others) other than tuberculosis. Most were working full time, a few part-time, but in all residual physical disabilities had required some change in work situation. Groups C and D were, respectively, hospitalized psychotic patients and outpatients with psychoneurotic reactions. The latter were all employed. Group E subjects were physically and mentally healthy, fully employed office or factory workers.

Test Procedure: All subjects were placed on bed rest in quiet surroundings, until at least two successive systolic blood pressure readings were the same, usually 30 to 45 minutes. Failure to obtain an accurate basal blood pressure is the chief source of error in the test. If the basal reading was under 110 mm., 0.05 mg. of epinephrine, diluted in a tuberculin syringe, was injected intravenously and systolic blood pressure followed every half minute for 10 minutes. If the pressure was over 110 mm., only 0.025 mg. was given.

When the blood pressure returned to basal level, usually within 10 minutes after injection, 10 mg. of mecholyl chloride was injected intramuscularly, and the systolic blood pressure again followed every half minute for the first four minutes, every one minute thereafter for the 25 minute test period.

Prior to each injection, the patient was told what symptoms to expect, which are common to all subjects. After each injection, he was asked what

TABLE I
AUTONOMIC GROUP AND TYPE OF PATIENT

	Patient Groups*				
Autonomic Group	A	B	C	D	E
2-3 "Normal" C.S.R.	5	4	0	0	12
1 & 4 Increased C.S.R.	4	4	3	9	0
6 Decreased C.S.R.	3	2	5	2	0
7 Abnormal C.S.R.	0	2	4	1	0

*A—Tuberculosis patients, B—Other chronic disease, C—Psychotic reactions, D—Psychoneurotic reactions, E—Healthy controls.

additional symptoms he felt, if any. Usually the patient volunteered this information if his response was excessive.

The test was not done on any person for whom either mecholyl or epinephrine would usually be contra-indicated. Atropine was always available to combat untoward cardiac complications due to mecholyl, but in over 350 tests, we have never needed it. Because of marked increase in all secretions following mecholyl, it was anticipated that in the tuberculous patients, cough would be increased and we might even obtain more sputum for examination in those with no or scanty expectoration. This did not prove true, however. In one tuberculous patient with residual bronchiectasis producing one cup per day, there was less cough during the test than during the course of pneumoperitoneum refill.

Psychiatric examinations were done independently, the psychiatrist knowing neither the patients' medical history nor results of autonomic testing.

Results

Although the number of patients in each group is small, study of Table I reveals two, not unexpected results. First, less than half the tuberculous

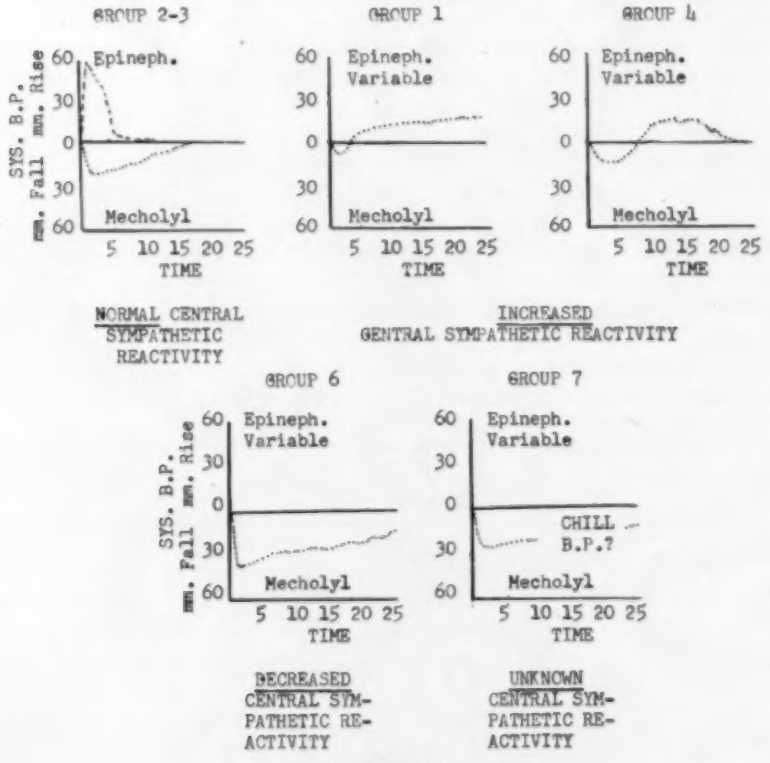

FIGURE 1

patients had a "normal" response, while all healthy controls fell in the "normal" group and all mental patients had abnormal responses. Second, the number and type of abnormality was essentially the same, in both the tuberculous and other chronic disease patients, suggesting that the etiology of the illness was not a distinguishing feature.

As we have previously found to be true of the total group of 135 subjects tested, there was no correlation between autonomic response and nutrition (Table II). All healthy controls, with "normal" Central Sympathetic Reactivity (C.S.R.), were adequately nourished, but so too were 18 mentally ill and nine chronic disease patients with "abnormal" C.S.R.

There was similar lack of correlation of autonomic response and presence of infection, estimated by sedimentation rate determinations of 70 unselected patients. Corrected sedimentation rates are shown in Table III, which reveals scattering of rapid rates throughout all autonomic groups. In fact, the greatest number of normal rates occurred in Group 6 patients, most of whom had severe psychotic reactions. There was no closer correlation in the tuberculous patients. Of the five with "normal" C.S.R., two had rapid rates; of the seven with "abnormal" C.S.R., rates were within normal limits in four. Lack of correlation was shown even more clearly in 11 patients with elevated sedimentation rates, who had repeat autonomic and sedimentation rate tests. In these 11, although the sedimentation rate fell to normal, the autonomic test continued abnormal.

When originally diagnosed all tuberculous patients had essentially the same far advanced cavernous disease. At the time of testing all were classified quiescent, apparently arrested, or arrested. The group is too small to determine correlations between number of sanatorium admissions, duration of hospitalization, duration of disease and results of autonomic testing. However, there was one finding of interest. The group represents 26 discharges. Of those with "normal" C.S.R. there was only one irregular discharge; nine were with medical advice. The one self-discharged patient was dissatisfied with lack of sanatorium personnel during the war and promptly put himself under private out-patient care.

The fact that there was greater correlation of the test with type of discharge than with physical condition suggested that psychological factors rather than somatic ones were responsible for abnormal test responses. To clarify this point psychiatric examinations were made to determine why the test curves of more than one half the chronically ill were similar to

TABLE II
AUTONOMIC GROUP AND NUTRITIONAL STATE

Autonomic Test	Groups A and B			Groups C and D		
	Good	Poor	Obese	Good	Poor	Obese
"Normal" C.S.R.	7	2	0	0	0	0
"Abnormal" C.S.R.	9	4	2	18	5	1

those of the mental patients. Psychiatric evaluation of three patients, one with increased, one with decreased, and one with "normal" Central Sympathetic Reactivity are given as typical examples.

Increased Central Sympathetic Reactivity (Figure 1, Group 4)

Case 1: A 30 year old male, with onset of tuberculosis at 12 years of age had two hospitalizations totalling six and one-half years, one discharge with advice, one without At time of examination, he was receiving pneumoperitoneum. Sputum had been negative on culture for three years. Occasional small hemorrhages, the last 18 months prior to autonomic testing, were attributed to bronchiectasis, demonstrated by bronchography. Autonomic testing revealed increased C. S. R. with moderate epinephrine precipitated anxiety, which the patient interpreted as a feeling of anger. Summary of psychiatric findings follows.

"The psychiatrist had met the patient socially several times and he always appeared happy, even jolly. Psychiatric examination revealed a young man full of hostilities, resentments, fears and feelings of insecurity. His greatest feelings of hostility were toward the sanatorium. While appreciating his medical treatment, he was most resentful that his school life had been interfered with and no one at the sanatorium had made any effort to help him with occupation or education. It was through his own efforts he contacted the American Correspondence School and began working for his high school diploma. (Incidentally this course had not yet been completed).

"He was hostile toward his employers, as he felt he did not receive a fair deal, due to the fact that he did not have proper formal education. He also felt discriminated against because he did not receive the salary as bookkeeper that the truck drivers and other physically capable men did. He resented the oversolicitude of his parents, especially the mother. He felt she used his illness as an excuse to keep him by her side as her errand boy.

"The patient not only felt insecure because of his lack of formal education but lived in constant dread of returning to the sanatorium. He also felt stigmatized and was fearful his fellow workers would find out he had tuberculosis and thus shun him. He was even afraid to cough, if he had a common cold.

"This patient is not mentally ill in the sense that he needs psychiatric hospitalization. However, he is emotionally poorly adjusted to his disease, his job, and his family."

Comment. This man illustrates many of the problems common to most patients with tuberculosis. Being unwilling to admit many of his hostilities, he is unable to handle them and instead presents a carefree, jolly "front" to the public. The increased C.S.R. of the autonomic test corroborates this "over-compensation." He is considered a "good" patient by his doctors, because he keeps the rules and "covers" his hostilities. In handling his hostilities, he is doing no better than the psychiatric out-patients with psychoneurotic reactions, most of whom also show increased C.S.R. (Table I, Group D)

TABLE III

AUTONOMIC GROUP AND SEDIMENTATION RATES

Sed. Rate mm./60 min.	Group 2 Normal C.S.R.	Groups 1-4 Incr. C.S.R.	Group 6 Decr. C.S.R.	Group 7
0 - 19	10	10	20	3
20 - 39	7	6	3	3
40 - 59	3	3	1	0
60 or more	0	1	0	0
TOTAL	20	20	24	6

Decreased Central Sympathetic Reactivity (Figure 1, Group 6)

Case 2: A 38 year old white female, with onset of tuberculosis at 33 years of age had three hospitalizations, totalling two years, two discharges without advice, one with. At time of examination, she had recently completed five months anti-microbials which had been given when an obliterative pleuritis had forced abandonment of pneumothorax. Sputum had been negative on culture for eight months and x-ray films had been stable for six months. Summary of psychiatric findings follows.

"She has never developed any judgment or foresight. Her method of handling any stress situation is to expect some public agency to offer financial assistance. She was one of 12 children. Her father was a W.P.A. worker, when they did not receive out and out public assistance, so naturally she expects assistance when and how she feels it her just due. She has remained married to an alcoholic, who for the past five years has spent much of his time in jail, and has five children by him, even though she says he has never worked and supported the family. With perhaps some basis in fact, she gives neglect of her children as her reason for leaving the sanitarium without advice. At times she unconsciously recognizes her inadequacies. Her reaction then is to feel martyred, sit down and weep, waiting for someone to come to her rescue, preferably with money.

"Tentative diagnosis is 'inadequate personality.' She is depressed, but not deeply so. Psychiatric hospitalization is not indicated at this time, but she would be benefited by out-patient guidance."

Comment. This patient's limited effort-making capacity is reflected by her decreased C.S.R., a response which is most often found in hospitalized mental patients, irrespective of psychiatric diagnosis, as well as alcoholics with or without tuberculosis. As a group, these patients put forth little sincere effort, as shown by their failure to cooperate in their own behalf, whether they are physically or emotionally sick. Free out-patient guidance was arranged for Case 2, but she failed to keep appointments. Perhaps, her autonomic imbalance makes it impossible for her to put forth more effort.

Normal Central Sympathetic Reactivity (Figure 1, Group 2)

Case 3: This 49 year old white female had always been in excellent health until 40 years of age. Since then she has had four sanatorium admissions, totalling five years. Each discharge was approved, she was checked at home by her family physician and apparently followed carefully a program of limited activities. Yet, a few months after each of the first three discharges, she relapsed, new and more extensive disease appearing on each readmission. On the fourth admission, pneumoperitoneum was initiated, in addition to the anti-microbials she had previously received. At the time of testing she had been receiving pneumoperitoneum for 30 months. Sputum had been negative on culture for 18 months. X-ray films had been stable for eight months, this being the longest period of stability since onset of her disease. Summary of psychiatric findings follows.

"The patient does not seem to be particularly upset concerning her physical condition. She is surprised that she has stayed out of the sanatorium for this period of time. She feels secure because she knows that she will be readmitted any time it is necessary and at least, as she put it, at the present time she has more friends and is happier in the sanatorium than on the outside. She is at a loss to know how to be of use on the outside, but she does feel that she can be helpful to other patients in the sanatorium. She seemed to rather enjoy this dependency, especially to enjoy the fact that she had no responsibilities.

"This patient shows no evidence of mental disease. The reason for psychiatric referral is unknown!"

Comment. This case illustrates how closely clinical evaluation of emotional imbalance and autonomic testing agree. The reasons this patient had a "normal" autonomic response are obvious. Unlike Case 1, there is no evidence of resentments or hostilities. Unlike Case 2, there are no unconscious feelings or guilt stimulated by dependency. She accepts both the disease and the dependency and derives satisfactions from both. She there-

fore makes an "ideal" sanatorium patient. One wonders if her attitude has anything to do with her relapses.

Comment

Since autonomic testing of the chronic disease patients was done when their illnesses were at least partially controlled, it is impossible to determine whether or not their psychophysiologic balance influenced their original disease. Theoretically, when abnormally severe physical symptoms are evoked by sympathetic or parasympathetic stimulation, this imbalance would contribute to "lowering resistance." Serial testing during various stages of illness might clarify this point.

The fact that almost two-thirds of the chronic disease patients had abnormal responses, although in each case the original disease had been stabilized, suggests that these patients had not received the complete medical care they needed. Since many workers with mental patients have shown that "abnormal" responses can be changed to "normal" ones by psychotherapy and other psychiatric therapies, it should be possible to accomplish the same thing for those not frankly mentally ill. The use of reserpine and chlorpromazine for those with severe autonomic test imbalance may be as useful adjuncts in tuberculosis, as they are in mental illnesses.

Wilmer[6] rightly deplores the inability to date "to define the patient population at risk from the standpoint of self-discharge." Testing autonomic responses, one facet of the total patient, may help in the definition of this group.

SUMMARY

1. Autonomic testing to determine Central Sympathetic Reactivity (Funkenstein test) was done on five groups of 12 subjects each: tuberculous patients, other chronic disease patients, out-patient psychoneurotic reactions, in-patient psychotic reactions, and healthy controls. Psychiatric examinations were done independently.

2. All healthy controls showed "normal" autonomic test responses. More than half, both tuberculous and other chronic disease patients had "abnormal" responses. Type of abnormality was essentially the same whether the patient had tuberculosis or some other chronic physical disorder.

3. There was no correlation of test response and (a) nutrition, (b) sedimentation rate, or (c) original disease. The tuberculous patients had been discharged from the sanatorium 26 times. There was a definite trend toward "normal" Central Sympathetic Reactivity in those who had had discharges with medical advice.

4. Brief case histories and psychiatric evaluation are presented to illustrate the three basic types of response: "normal" Central Sympathetic Reactivity, decreased C.S.R. and increased C.S.R. Our results suggest that many chronic disease patients, including those with tuberculosis, would be benefited by psychotherapy perhaps with reserpine or chlorpromazine as adjuncts.

5. The possibility of using autonomic testing to help differentiate the "self-discharge risk" is suggested.

RESUMEN

1. Las pruebas autonómicas para determinar la reactividad central simpática (reacción de Fukenstein) se hicieron en cinco grupos de 12 personas cada uno: enfermos de tuberculosis, otras enfermedades crónicas, reacciones psiconeuróticas en externos, reacciones psicóticas en internados y control entre sanos. Los exámenes psiquiátricos se hicieron independientemente.

2. Todas las personas sanas mostraron reacciones autonómicas "normales." Más de la mitad entre los tuberculosos y otros enfermos crónicos tuvieron respuestas "anormales." El tipo de anormalidad fué esencialmente el mismo así tuviese el paciente tuberculosis u otra afección crónica.

3. No hubo correlación entre la reacción y: (a) la nutrición, (b) la sedimentación globular, o (c) la enfermedad original. Los enfermos de tuberculosis habían sido dados de alta del sanatorio 26 veces. Hubo una definida tendencia hacia "normal," reactividad simpática entre los que salieron con acquiescencia médica.

4. Se presentan breves historias clínicas y estimaciones psiquiátricas para ilustrar los tres tipos basivos de respuesta: Reactividad central "normal," Reactividad central simpática disminuida y la aumentada. Nuestros resultados sugieren que muchos enfermos crónicos, incluyendo los de tuberculosis, se beneficiarían por la psicoterapia probablemente mediante el uso de la reserpia, la cloropromazina conagregados.

5. La posibilidad de usar las pruebas autonómicas para ayudar a diferenciar el "riesgo de las altas espontáneas," se sugiere.

ZUSAMMENFASSUNG

1. An 5 Gruppen von je 12 Personen wurde eine autonome Testung zur Bestimmung der zentralen symphatischen Reaktionsbereitschaft vorgenommen (Funkenstein-Test): Es handelte sich um Kranke mit Tuberkulose, mit anderen chronischen Erkrankungen, ambulante Fälle mit psychoneurotischen Reaktionen und stationäre mit psychotischen Reaktionen und um gesunde Kontrollen. Unabhängig davon wurden psychiatrische Prüfungen vorgenommen.

2. Alle gesunden Kontrollfäkle zeigten "normale" autonome Test-Reaktionen. Mehr als die Hälfte sowohl tuberkulöse als auch andere chronische Krankheitsfälle hatten "abnorme" Reaktionen. Die Art der Abweichung von der Norm war im wesentlichen dieselbe, gleichgültig, ob der Patient eine Tuberkulose hatte, oder irgend eine andere körperliche Störung.

3. Es bestand keine Beziehung zwischen dem Ausfall des Testes und a) der Ernährung, b) der Blutsenkung oder c) der Grundkrankheit. Die tuberkulösen Patienten waren 26 mal aus dem Sanatorium entlassen worden. Es bestand eine deutliche Neigung zu "normaler" zentraler

sympathischer Reaktionsbereitschaft bei denjenigen, die mit ärztlicher Zustimmung entlassen worden waren.

4. Es werden kurze Krankengeschichten und psychiatrische Beurteilungen vorgelegt zur Erklärung der 3 grundlegenden Typen der Reaktion: "normale" zentrale sympatische Reaktionsbereitschaft, herabgesetzte zentrale sympatische Reaktionsbereitschaft und erhöhte zentrale sympatische Reaktionsbereitschaft. Unsere Resultate lassen vermuten, dass viele chronische Krankheitsfälle einschliesslich solcher mit Tuberkulose Nutzen ziehen würden aus einer Psycho-Therapie, vielleicht mit Reserpin oder Chlorpromazin als Unterstützung.

5. Es wird die Möglichkeit angeregt, dass autonome Testverfahren dazu zu benutzen, das Risiko der "Entlassung aus eigenem Antrieb" zu differenzieren zu helfen.

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Malignant Mesothelioma of the Pleura

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Primary mesothelioma of the pleura is a controversial entity referring to a growth originating from the mesothelium, the cell layer covering the inner surface of the pleural, pericardial and peritoneal cavities which are derived from the celomic space of the embryo. Willis[1] denies their existence entirely and considers isolated masses of the pleura as metastatic deposits of some distant asymptomatic primary focus. Anderson[2] believes that in most instances neoplastic involvement of the pleura originates from a bronchial cancer, but he admits that in a small number of cases no intrapulmonary growth can be detected with a most meticulous examination. Ackerman and del Regato[3] are convinced that primary pleural mesothelioma exists but consider it a rare disorder. It may be benign appearing as a fibrous mass or malignant showing alveolar, follicular or papillary patterns. Even the latter types have a tendency to remain localized and to expand by invasion of the neighboring structures rather than by distant metastases. However, metastases do occasionally occur into almost any part of the body. Undoubtedly, benign primary tumors of the pleura have been repeatedly recognized;[4-9] therefore, the controversy between the various pathologists must refer to the malignant types which are difficult to classify on account of the great variability of their microscopic appearance.[4-12] These may be localized tumors varying from coin lesions[13] to huge masses occupying one hemithorax, or they may appear as diffuse thickening of the pleura with or without effusion. Their consistency varies from soft to hard, from brittle to elastic; their color has been described as white, grey, yellow, orange, red, or bluish. Their microscopic picture may resemble carcinoma, endothelioma, epithelioma, sarcoma, fibroma, fibromyoma and giant cell tumor.

Stout and Murray[10] believe to have solved the puzzle of the variable appearance of these tumors by demonstrating in tissue cultures that mesothelioma cells can develop into solid, tubular, or glandular structures of epithelial character as well as into mesenchymal tissues with fibroblasts, collagen, and reticulum fibers. Sometimes one form of growth predominates but more often there is a mixture present causing a great variability of different sections of the same tumor. Other authorities,[2] however, are of the opinion that bronchogenic cancers may reveal all the pathological features described as characteristic of mesothelioma. This confused status of the pathology of pleural tumor masses makes their clinical evaluation difficult and is apparently responsible for the scarcity and brevity of reports describing their symptomatology during lifetime which is in contrast to the extensive literature discussing their autopsy appearance. Nevertheless, the practicing physician will have to face from time to time the problem of dealing with such isolated pleural growth deserving the

name of malignant mesothelioma.

Considering the great variability of the pathological picture one should expect a multitude of clinical manifestations, laboratory and x-ray findings. It has been stated that some benign types of pleural mesothelioma are asymptomatic and only accidentally discovered during an x-ray investigation. If symptomatic, these tumors are usually responsible for various types of discomfort in the chest and epigastrium among which the typical pleurisy pain aggravated by coughing, sneezing and deep breathing is quite uncommon. Various respiratory disturbances may occur such as dyspnea, cough, hemoptysis and mucoid, purulent or blood-streaked sputum; digestive discomfort may be present in the form of anorexia, nausea, vomiting, belching and epigastric fullness; general malaise may be noticeable with fever, chills, anemia and weight loss. Clubbing of fingers and osteoarthropathy have also been reported.[7, 8, 11] In the malignant cases invasion of the diaphragm, the chest wall, the pericardium and the peritoneum is responsible for additional symptomatology. Clinical and roentgenological findings are either those of single or multiple solid tumors or of pleural effusions with various types of exudates that are resistant to a conservative treatment.

In contrast to those features considered to be characteristic of mesothelioma, the presented case shows quite a few different findings worth reporting. The diagnostic difficulties of this disease are clearly demonstrated by the fact that it escaped recognition over a period of several

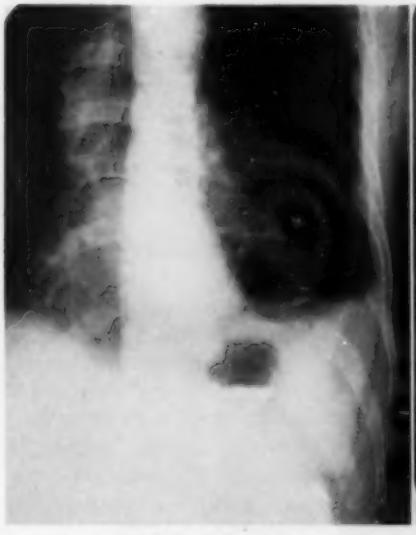

FIGURE 1

FIGURE 2

Figure 1: Chest film of August 1952, showed pneumothorax and small fluid level. Left hemidiaphragm was slightly elevated (see position of "magenblase") and was immovable.—*Figure 2:* Chest film of August 19, 1954: destruction of lower ribs with soft tissue mass adjacent to them.

years in spite of the most thorough investigations including exploratory laparotomy and thoracotomy. The patient was seen by a number of physicians including specialists of almost any field of medicine.

Case Report: A 57 year old male refinery foreman was treated on May 5, 1950, for acute posterior coronary artery occlusion with myocardial infarction.

Marital and family history were non-contributory. In 1918 he had suffered from a severe attack of influenzal pneumonia. For about 20 years he had been suffering from spells of indigestion with "gas pain" in the left upper abdomen and mucus in the stool.

FIG. 3

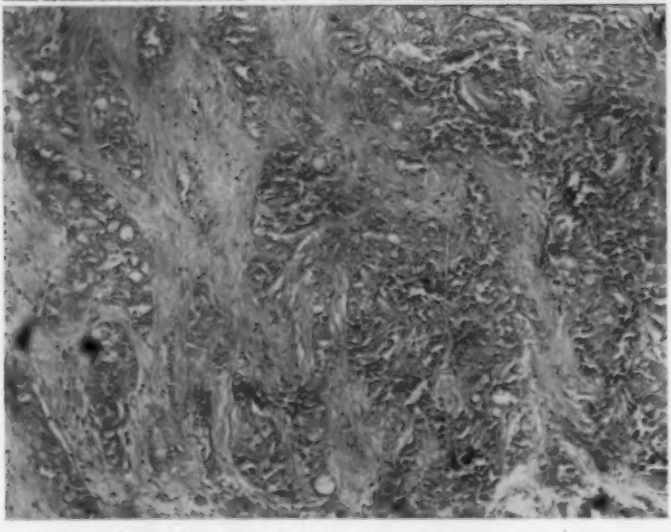

FIG. 4

Figure 3: Section of first biopsy: alveolar pattern invading dense fibrous tissue. Dr. Vernie A. Stembridge (X 48 magnification).—*Figure 4:* Section of second biopsy: medullary pattern. Dr. Vernie A. Stembridge (X 110 magnification).

These attacks of bowel dysfunction were frequently associated with urticaria and attributed to an irritable bowel syndrome associated with food allergy. The heart attack proved to be severe and was followed by a prolonged period of disability with persistent hypotension and marked Q and T wave changes in the electrocardiogram. There remained a stubborn discomfort from the left lower chest as well as the left epigastrium. It was difficult to decide if this was an aftermath of the occlusion or an exaggeration of the previously encountered left flexure syndrome. The patient himself attributed it mostly to the intake of incompatible food as well as to his constipation and gas formation. In the following years thorough clinical studies were repeated several times but no additional pathology could be elicited.

In April 1952, however, the discomfort from the left side of the trunk had become so severe that he consulted three large medical centers in succession. Here, he underwent thorough examinations, but only the previous diagnoses of old myocardial infarction of the diaphragmatic surface, functional bowel disturbance, food allergy and anxiety neurosis could be confirmed. Nevertheless, the treatment suggested on the basis of these investigations failed to bring him relief. Shortly after returning from these clinics to his home city, a routine fluoroscopic checkup revealed unexpectedly a left spontaneous pneumothorax with small fluid level and slightly deformed, elevated and immovable diaphragm. However, neither the collapsed lung nor the visible part of the pleura showed any abnormality (Figure 1). The air was aspirated together with the fluid; the latter contained five grams of protein per 100 cc. and quite a few cells, 80 per cent of which were lymphocytes and 20 per cent eosinophils. Smears, culture, guinea pig inoculation and special studies for tumor cells were unrevealing. The origin of the pneumothorax as well as the exact time of its onset could never be clearly elucidated. An x-ray film taken about four weeks prior to the accidental discovery of this disorder showed a completely normal chest. The patient himself attributed it to an accident which he had sustained in February 1952, when he slipped from a scaffold and tried to grab a brace to hold himself. At this time he felt a sudden severe pain in the left side. However, an x-ray film taken immediately following this fall had been entirely negative. The pneumothorax disappeared after several aspirations but the drawing and pulling pains persisted. It was worse in the evening after moving about all day and was temporarily relieved by bed rest as well as by intercostal nerve blocks.

In the following weeks a progressive deformity of the left hemithorax was noticed apparently caused by pleural contraction. It was so severe that he walked with his trunk bent over to the left and that he developed marked scoliosis with the convexity to the right. As this finding seemed to be an unusual sequela of a simple pneumothorax, an exploratory thoracotomy was advised in July 1953. This operation was preceded by bronchography and bronchoscopy which, however, yielded no additional information. The only finding at the time of the surgical exploration appeared to be an extreme fibrothorax which was treated with decortication. The pathologist noticed severe fibrous thickening of the pleura (Figure 3). The pericardium, the left lung and the subphrenic space were carefully palpated during the operation but no abnormality could be demonstrated. Unfortunately, these surgical efforts brought no relief and he then started to consult various chiropractors and cultists, but was unable to get help; neither did psychiatric consultation and shock treatment change his symptomatology. Contrary to expectations, the fibrothorax recurred and the scoliosis as well as the shrinking of the left hemithorax were soon worse than ever before. Physiotherapy and various muscular exercises did not improve the misery; neither did x-ray therapy of the bones and a brace prescribed by an orthopedic surgeon. In the meantime a considerable loss of weight and strength was apparent approaching the state of cachexia. This was to a large extent caused by the patient's attempt to relieve his "gas pains" by restriction of food as well as by excessive purging. After a neurosurgical consultation had yielded no new clues to his trouble, he underwent an exploratory laparotomy July 7, 1954, which revealed no pathology except masses of adhesions extending from the lower surface of the diaphragm to the spleen and the left flexure of the colon. These were severed but the course of the disease was not changed. The origin of his suffering remained obscure until August 19, 1954, when x-ray films revealed some osteolytic lesions as well as pathological fractures of the left lower ribs (Figure 2). Therefore, on September 14, 1954, another operation was performed (Dr. L. R. Lancaster) to obtain specimens of these destroyed bones. The microscopic examination showed "mesothelioma of the pleura" attached to the destroyed ribs (Dr. Ellen Furey, Pathologist, Hotel Dieu, Beaumont, Texas; Dr. Vernie A. Stembridge, University of Texas Medical School, Galveston, Texas) (Figures 4 and 5.) On November 26, 1954, he passed away in a state of extreme cachexia. Permission for an autopsy was not obtained.

Comment: It must be admitted that the presented case does not fulfill all the requirements of the diagnosis of primary mesothelioma of the pleura

because no autopsy was available excluding any other primary malignancy: Nevertheless, the latter disorder is unlikely on account of the surgical explorations, the pathological findings and the most complete clinical investigations. It may be argued that this tumor did not originate from the mesothelium itself but from the peripheral pulmonary tissue.[2] This possibility would be of much more concern to the pathologist than to the clinician. The latter is mainly interested in the fact that apart from the absence of respiratory symptoms no intrapulmonary tumor could be found on x-ray films before, during and after pneumothorax and with bronchoscopy, and palpation of the lung during exploration. Thoracotomy showed only an extensive pleural thickening with adhesions.

This growth and similar ones described in the literature should at least deserve special recognition as a clinical entity in order to facilitate the diagnosis even if their origin is uncertain. Any persistent, or recurrent pain and discomfort from one side of the trunk not explainable by abnormal findings of the thoracic cage, the intrathoracic and intraabdominal organs, the spine, or the central and peripheral nervous system should alert the investigator to the possibility of pleural mesothelioma. If the x-ray film of the chest is entirely negative one has to realize that the initial lesion may be in the hidden diaphragmatic or mediastinal section of the pleura. In addition, Rabin[14] has emphasized that the majority of pleural x-ray shadows are caused by effusions or by inflammatory granulation tissue, and that even an extremely thickened and indurated pleura may fail to be visible on the x-ray film. Therefore, it seems plausible that in the initial stage a diffusely growing pleural tumor without effusion may not possess enough opacity to be recognized roentgenologically.

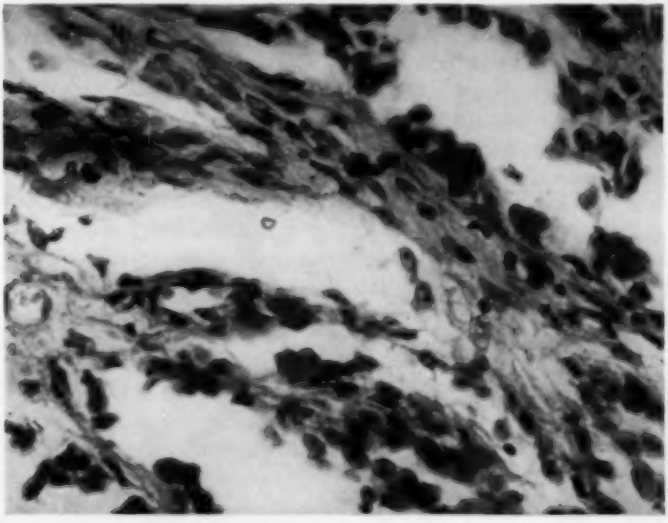

FIGURE 5: Section of second biopsy: alveolar pattern removed from skeletal muscle tissue. (X 473 magnification).

One could speculate about the connection between an infarction of the diaphragmatic surface of the heart and a tumor manifesting itself initially in the phrenicocardiac region. However, the heart attack had all the features of a classical coronary occlusion, and there was never any pericardial involvement in spite of repeated clinical, cardiographic and roentgenologic investigations. Therefore, one must assume that this association is fortuitous. Unfortunately, there was no clearcut clinical evidence of the beginning of the pleural tumor, because the various diseases leading to pain and discomfort in the left hemithorax and upper abdomen overlapped each other. Initially, the patient was suffering from gastrointestinal spasms, left flexure syndrome, food allergy and mucous colitis for several decades. Later, after the sudden coronary occlusion he seemed to have an anginal type of distress which could be easily correlated with the persistence of the electrocardiographic abnormalities. In the final stage all these disorders caused symptoms concomitantly with those originating from the tumor predominating.

Of considerable interest was the spontaneous pneumothorax as the initially presenting sign of the tumor. Such occurrence has apparently not been described in the literature. It is well known that spontaneous pneumothorax can occasionally appear in the beginning as well as during the course of a bronchogenic cancer, and that it is more frequently observed in metastatic pulmonary sarcomas.[15] It is supposedly due to the infiltration of the lung bordering the pleura by malignancy followed by tissue destruction leading to bronchopleural fistula. A similar mechanism could be operating in mesothelioma which invades the parenchyma from the periphery.

In addition to the spontaneous rupture of the lung our case was distinguished from the majority of the mesotheliomas reported in the literature by the formation of a progressing constrictive pleurisy leading to a severe deformity of the chest as well as the whole body. Such a finding depends obviously on the character of the tumor: a solid growth of tubular and glandular elements will either appear as an expanding mass or as an intractable pleural effusion while the formation of mesenchymal tissue with innumerable fibrous layers will lead to chronic fibrothorax. The latter form of growth was present in our patient with such a marked degree of fiber production that at first the diagnosis of benign constrictive pleurisy and later of massive peritoneal adhesions was entertained and that the true character of the disease was not recognized until bone destruction occurred.

SUMMARY

A case of a malignant mesothelioma is described starting in the diaphragmatic portion of the pleura and invading the left hemidiaphragm and the peritoneal cavity. Malignant pleural tumor is a definite clinical entity even if its pathological classification remains a matter of speculation.

Persistent or recurrent discomfort from one hemithorax or one side of the epigastrium may be the initial symptom of such a growth in the absence of positive roentgenological findings.

Spontaneous pneumothorax may occur at any time during the course of this disease or may be the initial feature.

Mesothelioma must be included in the differential diagnosis of solid intrathoracic masses, persistent pleurisy with effusion, and progressive fibrothorax.

RESUMEN

Se describe un caso de mesotelioma que empezó en la parte diafragmática de la pleura e invadió el hemidiafragma izquierdo así como la cavidad peritoneal. El tumor maligno de la pleura es una entidad clínica definida aunque su clasificación patológica siga siendo motivo de especulación.

Las molestias persistentes o recurrentes en un hemitórax o en un lado del epigastrio, pueden ser el síntoma inicial de tal neo formación en ausencia de hallazgos positicos a los rayos X.

El neumotórax espontáneo puede ocurrir en cualquier tiempo en el curso de esta enfermedad o puede ser el accidente inicial.

El mesotelioma debe incluirse en el diagnóstico diferencial de las masas sólidas intratorácicas o cuando hay pleuresía persistente con derrame y fibrotórax progresivo.

RESUME

L'auteur décrit un cas de mésothéliome malin qui, son point de départ étant localisé à la portion diaphragmatique de la plèvre, a fini par envahir l'hémi-diaphragme gauche et la cavité péritonéale. La tumeur pleurale maligne est une entité clinique bien certaine même si la classification pathologique reste matière à discussion.

La gêne continue ou intermittente d'un hémithorax ou d'un côté de l'épigastre peut être la manifestation initiale en l'absence de constatations radiologiques positives.

Un pneumothorax spontané peut survenir à tout moment de l'évolution et peut réaliser le symptome initial de l'affection.

Le mésothéliome peut être compris dans le diagnostic différentiel des masses intrathoraciques, des épanchements pleuraux chroniques, et du fibro-thorax progressif.

ZUSAMMENFASSUNG

Beschreibung eines Falles eines malignen Mesothelioms, ausgehend vom Zwerchfellteil der Pleura mit Durchsetzung der linken Zwerchfellhälfte und der Bauchhöhle. Der bösartige pleurale Tumor ist eine wohl abgegrenzte klinische Einheit, auch wenn seine pathologische Einordung eine Sache der Vermutung bleibt.

Anhaltende oder wiederkehrende Beschwerden auf einer Brustkorbhälfte oder einer Seite des Epigastriums können das Initial-Symptom eines solchen Wachstums sein bei Fehlen positiver röntgenologischer Befunde.

Ein Spontan-Pneumothorax kann zu jeder Zeit im Verlauf dieser Krankheit auftreten oder kann auch das initiale Merkmal sein. Ein Mesotheliom muss in die Differential-Diagnose einbezogen werden bei soliden intrathorakelen Massen, anhaltender Pleuritis mit Erguss und fortschreitendem Fibrothorax.

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Case Report Section

Hemorrhagic Pleural Effusion Complicating Infectious Mononucleosis

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Pleural effusion is an unusual complication of infectious mononucleosis. In the literature available to us the only previous case of pleural effusion occurring during an illness of infectious mononucleosis was reported by John B. Vander.[1] We were unable to find a report of infectious mononucleosis complicated by hemorrhagic pleural effusion so we are reporting the following case study: Mrs. B. H. is a white, married, female, 24 years of age, who was referred to St. Paul by Dr. Richard Zauner of Fargo, North Dakota. She arrived in St. Paul on October 21, 1955 and reported that she had been suffering from infectious mononucleosis for approximately three weeks. Dr. Zauner established the diagnosis by the clinical history and physical examination and the diagnosis was confirmed by the hematologist. In addition, there was an increasing heterophile antibody titre during the three weeks of her illness. At the onset of her illness in September of 1955 she had pleuritic pain in her right chest. This pain was associated with fever and respiratory distress. The pain became so severe that she was hospitalized. Physical examination on October 25, 1955 at the time of her admission to St. Luke's Hospital revealed her to be acutely ill. On physical examination there was limitation of movement of the right side of the chest and the physical findings of fluid were present over the right posterior lung fields. Dr. Zauner's report stated that she had enlargement of the spleen as well as slight enlargement of the liver during her stay at St. John's Hospital in Fargo. While confined there she had a daily elevation of her temperature and enlarged cervical lymph nodes were found.

The laboratory data from Fargo reported all agglutination titres were normal except for an increasing heterophile anti-body titre which reached a value of 1:224. The x-ray films of the chest revealed an infiltration at the right costophrenic angle which was considered to be pneumonic. This gradually subsided and had diminished at the time of her admission to St. Lukes Hospital in St. Paul.

Her family history was negative, social history excellent, past history revealed she had an appendectomy and cholecystectomy about four years before her admission to the hospital and that she had a repair of a meningocele at the age of one year. She has always been emotional and immature.

Laboratory examinations in St. Paul revealed hemaglobin 12.3 grams; red blood cell count 4,200,000; white blood cell count 10,600; with differential as follows: 21 polymorphonuclear cells; 4 stab cells; and 74 lymphocytes with one basophile. The lymphocytes were atypical and suggested infectious mononucleosis. The urine examination was negative and the erythrocyte sedimentation rate was 49 millimeters in one hour; this increased to 102 millimeters during the course of her illness. The blood chemistries were normal. The blood proteins were normal. The Thorn test was normal. The triple skin tests were negative and the tuberculin test was repeatedly negative. Blood cultures remained sterile. X-ray film revealed the presence of fluid in the right pleural cavity. A muscle biopsy and thoracentesis was performed by Dr. Coleman Connelly of St. Paul. The muscle biopsy and sternal bone marrow were negative. Fluid removed, from the pleural cavity appeared hemorrhagic. It was negative to bacteriological and cytological investigation. The Wassermann and agglutination tests were negative. The electrocardiograms, and blood chemistries were normal. The hemorrhagic effusion recurred promptly following thoracentesis. Dr. Connelly explored the right thoracic cavity on November 15, 1955, and found a large collection of hemorrhagic pleural fluid and a small indurated area in the right lung which was about the size of an adult ovary. This was removed and the chest closed. She made an uneventful convalescence. The pathologist reported the lesion as being a healed infarct. However, a second pathologist felt that the lesion represented a pleural reaction to infection.

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Endobronchial Hamartoma

A CASE REPORT

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According to Albrecht's definition in 1904, a hamartoma is a tumour-like malformation due to abnormal mixing or abnormal development of the normal tissue components of an organ. Since exploratory thoracotomy has become more common for undiagnosed circumscribed pulmonary lesions, peripheral hamartomata are no longer considered rare. Endobronchial hamartomata, on the other hand, are less common. In 1954, Young et al. described two cases of their own and found 24 others reported. Chardack and Waite (1953) reported an additional case, and Sutherland et al. (1953) another two. Little is known of the rate of growth of pulmonary or bronchial hamartomata. The following is a report of an additional (30th) case.

I. R., a white man aged 41 years was admitted to the Toronto Western Hospital on July 20, 1954. He was well until two months previously when he felt tired and developed slight cough with some green sputum. He was treated for several days at home and returned to work but found that his temperature rose each night to 101°. On June 3, an x-ray film of his chest showed the left upper lobe collapsed. He was admitted to another hospital and given a sulpha preparation. His condition improved; he felt stronger; gained six lbs. and his cough stopped. However, re-examination on July 8, showed a persistent collapse of his left upper lobe. This was confirmed by planograms which failed to show a tumour.

On physical examination there was dullness and reduced tactile fremitus and breath sounds over the left upper lobe but no other abnormality was found. At bron-

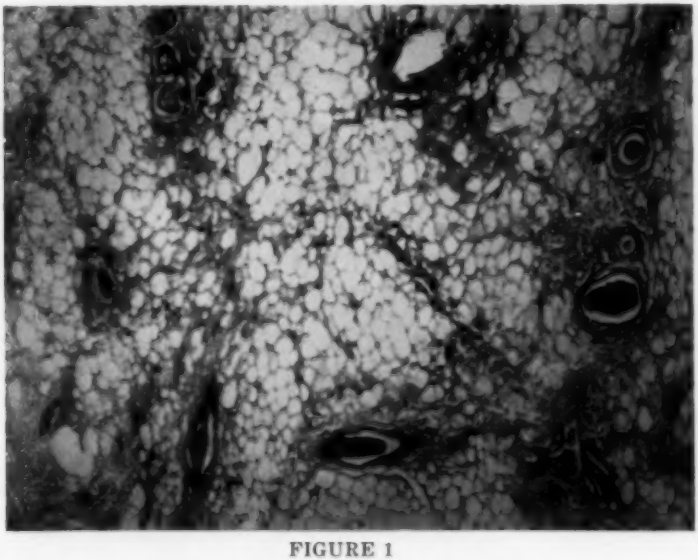

FIGURE 1

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choscopy on July 21, using a right angle telescope a smooth pale pink tumour was seen which hid the orifices of the bronchi to the upper and lower divisions of the left upper lobe. Because of its position no bite biopsy could be taken. Aspiration biopsy showed no malignant cells. It was believed to be a benign tumour.

At thoracotomy on July 28, 1954 (Dr. G. H. Joynt), the left upper lobe was collapsed. Left upper lobectomy was performed but the tumour could not be completely removed by this procedure since it arose in the tissue needed for the formation of the bronchial stump. The left upper bronchus was opened and the tumour was seen proximal to the carina between the bronchi to the upper and lower divisions. Biopsy with frozen section was made and hamartoma reported. Since the cause of his symptoms, namely the collapsed left upper lobe, had been removed and since it was a benign tumour it was decided not to proceed with pneumonectomy. Bronchial resection was considered but was not feasible because of dense adhesions and inflamed lymph nodes in the region of the pulmonary artery. The endobronchial part of the tumour was therefore removed and the remainder left behind in the bronchial stump. This was over-sewn with interrupted silk suture and the chest was closed. The post-operative course was normal.

Examination of the left upper lobe showed that the pleural surface was normal; the bronchi were dilated and contained purulent material. The lung parenchyma was dark red, firm and poorly aerated. The biopsy specimen showed tissue which consisted of mature adipose tissue and strands of loose fibrous tissue. Scattered throughout this were small round, oval or irregular gland spaces which were lined by a single layer of mucus-secreting epithelial cells of the bronchial type. In other glands the epithelium was flat and atrophic. The lumen of these gland spaces contained eosinophilic homogeneous material. A portion of a fibrous capsule could be seen surrounding this tissue. There was no evidence of proliferative activity or of malignancy. The appearance was characteristic of hamartoma (Figure 1). Section of the left upper lobe showed well marked bronchiectasis with loss of bronchial muscle. The lung parenchyma was atelectatic, partly fibrous and numerous focal collections of lymphocytes were seen. No tumour was found.

He recovered quickly from the operation and returned to work feeling perfectly well. Plain x-ray films and planograms on March 9, 1955. showed the left lower lobe expanded without sign of the tumour. On May 21, 1955, bronchoscopy was repeated. The lumina of the left main and lower bronchi were normal. Using a right angle telescope the remains of the hamartoma could be seen protruding from the upper division of the left upper lobe but on this occasion not hiding the orifice of the stump of the bronchus to the lower division.

Discussion

Hamartomata of the lung or bronchus are usually reported within lobes or lungs removed at thoracotomy or autopsy. In this case biopsy at thoracotomy showed conclusively that this was an endobronchial hamartoma. Part of it was intentionally left in the stump of the left upper bronchus because it is believed that hamartomata grow slowly. The cause of his disability has been removed by lobectomy. In his case pneumonectomy may never be necessary.

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Miliary Tuberculosis and Hodgkins Disease*

Case Report with Autopsy Findings

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Since Sternberg's[1] description of Hodgkin's disease in 1898, attention has been focused on the question of its relation to tuberculosis. Ewing's[2] dictum "tuberculosis follows Hodgkin's disease like a shadow" would lead one to believe that there is an etiological relationship between these two diseases. However, we now know that the occurrence of these two diseases in one individual is merely a coincidence.

It is interesting to note that Hodgkin's disease may resemble tuberculosis in many ways: hilar lymph node involvement may simulate the glandular enlargement of primary pulmonary tuberculosis; pleural involvement may be confused with tuberculous pleurisy with effusion; miliary type of Hodgkin's disease may be misdiagnosed as miliary tuberculosis; involvement of cervical lymph nodes may be confused with tuberculous cervical adenitis.

This report deals with a patient who had been known to have Hodgkin's disease for 10 years prior to the development of miliary pulmonary tuberculosis in October, 1952. The miliary tuberculosis was treated successfully with long term chemotherapy, streptomycin sulfate and para-amino-salicylic acid, and no trace of recognizable tuberculosis remained on autopsy examination. The primary cause of death was Hodgkin's disease and death occurred 11 years after this disease was originally diagnosed.

Case Report

C. L., a 58 year old white man was admitted to Glen Lake Sanatorium on October 10, 1952. His present illness apparently began in August, 1952, with irregular fever, ranging to 102° F. Cough with minimal amounts of sputum and night sweats developed about one week later. In addition, he had urinary symptoms which were felt to be due to urinary tract infection. On October 9, 1952, his temperature was 102.2° F. and he was transferred from the Minneapolis General Hospital to Glen Lake Sanatorium with a diagnosis of miliary pulmonary tuberculosis which had been confirmed by x-ray examination.

Past history indicated that he had been crippled by arthritis deformans for more than 30 years and had been followed at the Medical Clinic of the Minneapolis General Hospital regularly since 1937. On August 11, 1942, removal of a small tumor of the right side of the neck revealed Hodgkin's disease and for this he received deep x-ray therapy at the University of Minnesota Hospital. In November, 1948, he was found to have chronic glomerulonephritis and was placed on a low salt diet and

*From Glen Lake Sanatorium.

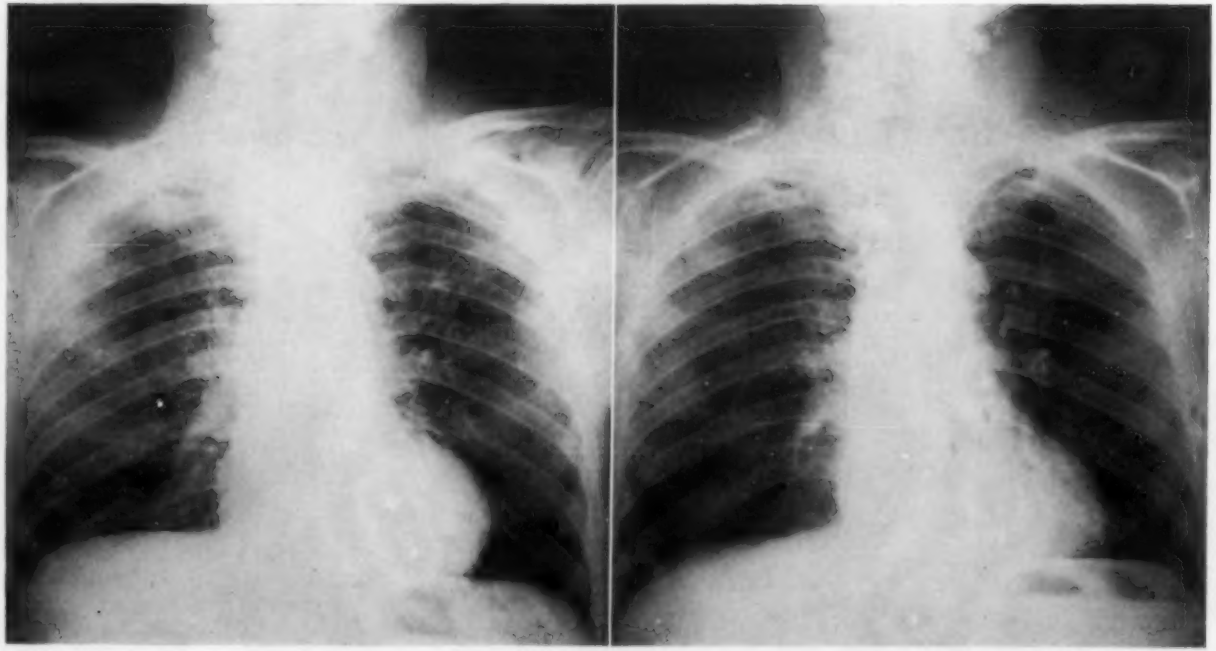

FIGURE 1 FIGURE 2

Figure 1: Chest film, October, 1952, before SM-PAS revealed diffuse granular infiltrations bilateral suggestive of miliary tuberculosis. Two gastric cultures were positive for tubercle bacilli.—*Figure 2:* Chest x-ray, June, 1953, after eight months of SM-PAS revealed complete disappearance of miliary tuberculosis.

received mercuhydrin injections weekly for ankle edema. There was no familial or contact history of tuberculosis.

On physical examination, he appeared to be in acute distress. He was crippled by deforming arthritis with partial ankylosis of all the joints of his extremities. Temperature was 101° F., pulse 88, respirations 26, blood pressure 118/88 mm. of Hg. Blood examination revealed hemoglobin of 8.8 gms., red blood cells 3,310,000. white blood cells 4,900 with neutrophils 72.5 per cent, lymphocytes 9.5 per cent, and monocytes 18 per cent. Blood sedimentation rate was 52 mm. in one hr. and the blood Wassermann test was negative. Urine was clear, acid, specific gravity 1.015, albumin 3+ and was negative for sugar. Urinary sediment revealed several hyaline casts with a few granular casts and one to three white blood cells per high power field. Sputum smears and one sputum culture were negative but two gastric cultures were positive for acid-fast bacilli in October, 1952. X-ray film examination of the lungs on admission revealed diffuse, granular densities consistent with miliary pulmonary tuberculosis (Fig. 1).

Hospital course: He received streptomycin sulfate, 1 gram daily and PAS 9 grams daily for the first six months. Streptomycin sulfate was then given for an additional six months in a dosage of 1 gram twice a week with daily PAS. Two blood transfusions were given soon after admission. Blood report on January 20, 1953, revealed hemoglobin 10 gms., red blood cells 3,240,000. white blood cells 3,200 with neutrophils 65 per cent, lymphocytes 21 per cent, monocytes 13 per cent, and basophils 1 per cent. The mean corpuscular volume was 106 cubic microns, volume index 1.22, color index 1, mean corpuscular hemoglobin 31 micromicrograms, mean corpuscular hemoglobin concentration 26 per cent and hematocrit 34 per cent. Clinical and x-ray improvement were demonstrated within a few months. Chest x-ray film on June 15, 1953, revealed complete disappearance of the miliary infiltrations (Fig. 2). Tubercle bacilli could no longer be recovered by culture of sputum and gastric contents.

However, he developed cyclic fever with headache, nausea, anorexia, heartburn and abdominal cramps thought to be due to an acute exacerbation of chronic nephritis. He developed uremia with temperature to 104° F., drowsiness, followed by unconsciousness and generalized edema. Blood pressure was 116/66 mm. of Hg. and urine examination revealed albumin 3+ with numerous granular casts. Blood urea nitrogen rose to 78.2 mgs. per cent and the blood plasma-proteins revealed a total of 4.0 grams with albumin 2.6 grams and globulin 1.4 grams. He was critically ill at that time. Treatment with blood transfusions, intravenous feedings and diuretics resulted in temporary recovery from the uremia with reduction of the blood urea nitrogen to 23 mgs. per cent. However, the severe anemia persisted in spite of numerous blood transfusions. Blood examination in October, 1953, showed hemoglobin 8.3 gms., white blood cells 2,050 with neutrophils 55 per cent, lymphocytes 24.5 per cent, monocytes 19.5 per cent and eosinophils 1 per cent. Blood sedimentation rate was 18 mm. in one hr. Bone marrow puncture, which had been unsuccessful in October, 1952, because of arthritic changes, was repeated successfully in December, 1953, and

revealed a non-diagnostic bone marrow. Streptomycin sulfate and PAS were discontinued in October, 1953, because of the persistent leukopenia. At this time the spleen was also found to be enlarged. His general condition rapidly deteriorated, with headache, joint pains, abdominal pain, vomiting and, subsequently, generalized edema. Blood report on December 22, 1953, revealed hemoglobin 7.2 gms., white blood cells 1,350 with neutrophils 58 per cent, lymphocytes 22 per cent, and monocytes 20 per cent. He died on December 23, 1953.

Postmortem examination of the lungs, spleen and lymphatic system were of special interest.

Lungs: The lungs were extremely boggy on palpation and foamy liquid could be expressed from the trachea. There was diffuse edema and ill-defined grayish, patchy consolidation, suggesting bronchopneumonia, was present. Nothing recognizable as tuberculosis was seen grossly. Microscopically, several sections revealed acute bronchopneumonia with masses of bacteria in some bronchi and alveoli. No microscopic evidence of tuberculosis was found.

Spleen: The surface was moderately deformed as the result of subcapsular nodules. On palpation, these nodular areas were somewhat firmer than the adjacent parenchyma and they ranged in size from 1 to 4 cms. in diameter. These nodular areas were found to be poorly circumscribed with indistinct edges which tended to blend with the adjacent parenchyma. Microscopically, the large, vague nodules showed reticulum hyperplasia with a few mitotic figures and were suggestive of Hodgkin's disease.

Lymphatic system: There were a few slightly enlarged, moderately firm, black nodes in the hilus of each lung. However, large masses of confluent, soft lymph nodes measuring up to 5 cms. in diameter were noted extending from the level of the diaphragm to the pelvis. Microscopically, these nodes showed loss of normal pattern with mild fibrosis and what appeared to be edema. Most of the cells were small, mature lymphocytes, but a few areas showed larger cells with an occasional giant cell. These cells were considered diagnostic of Hodgkin's disease.

Anatomical diagnosis: Hodgkin's disease: bronchopneumonia, severe; and arthritis deformans.

Discussion

The occurrence of miliary tuberculosis and Hodgkin's disease in one individual is rare. Bernard, et al[3] in 1949 reported a case of probable miliary tuberculosis with Hodgkin's disease treated with streptomycin. Smith[4] reported in 1952 that the three year survival rate of 106 patients with uncomplicated miliary tuberculosis was approximately 70 per cent when treated with SM-PAS. Now, with the addition of isoniazid, the prognosis for recovery is estimated to be 90 per cent or more. Williams[5] reported a 95 per cent survival rate at 18 months of 60 patients with uncomplicated miliary tuberculosis following treatment with SM-INH or SM-INH-PAS. It is generally agreed that the addition of INH will prevent the development of meningitis in patients with miliary tuberculosis.

The duration of life with Hodgkin's disease is variable and the prognosis

of untreated Hodgkin's disease is poor, Ewing[2] reported an average life expectancy of 18 months; Craft[6] found that 6 per cent of 52 untreated patients survived five years but no untreated case had survived 10 years. Nice[7] reported that 25 per cent of patients receiving radiation therapy survived five years or longer and 11 per cent had survived 10 years. The patient we are reporting survived 11 years after diagnosis had been verified.

It is worth noting that chemotherapy, SM-PAS, apparently had no influence on the course of the Hodgkin's disease.

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Bronchiectatic Sequelae of Pulmonary Tuberculosis and Its Subsequent Complications

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The following case is presented for the interesting sequelae of far advanced, bilateral pulmonary tuberculosis.

In the pre-chemotherapy era, the patient to be discussed would probably have died rather promptly. At the present time, many of these formerly hopeless cases survive, but with extensive residual pulmonary destruction. Bronchiectasis is one form this destruction may assume. The following case report represents the sequelae of bronchiectasis and subsequent complications.

Case Report: P. M. J., a 15 year old colored female, was admitted to Battey State Hospital on March 21, 1953, with the complaint of loss of appetite and productive cough.

In view of the symptomatology presented and history of her father dying of tuberculosis approximately one year previously, tuberculosis was strongly suspected and a chest x-ray was made. Chest x-ray revealed pulmonary disease and subsequent sputum studies were positive for acid-fast bacilli. She was admitted to this hospital.

Past history revealed the usual childhood diseases, including measles, whooping cough and mumps. No other significant past history was elicited from the patient.

The family history was essentially negative, with the exception of her father, who died of pulmonary tuberculosis one year previously.

The physical examination revealed a poorly nourished, cachectic, acutely ill, colored female. Temperature on admission 102.2° F. and pulse 140. Examination of the chest revealed diminished breath sounds in the right upper lung field, with dry and moist rales scattered throughout both lung fields. The remainder of the physical examination was essentially negative.

Laboratory data: The sputum was positive on direct smear, Gaffky IV. White blood count was 6,300, with a hemoglobin of eight and one-half grams and a hematocrit of 28 per cent. The sedimentation rate was 32. Urine analysis revealed one-plus albumin.

Chest x-ray: The right lung showed dense, soft, scattered infiltration throughout the entire right lung, and the greater part of the upper lobe had excavated. The left lung showed dense, soft, scattered shadows of infiltration from the first interspace to the level of the diaphragm. (Figure 1)

The admission diagnosis was pulmonary tuberculosis, bilateral. Classification: Far advanced, D. Prognosis: Poor.

This patient was placed on streptomycin, para-aminosalicylic acid, and Isoniazid on admission. Streptomycin was discontinued after approximately three months, due to drug reaction. She remained on para-aminosalicylic acid and Isoniazid and in April, 1953, the sputum converted and

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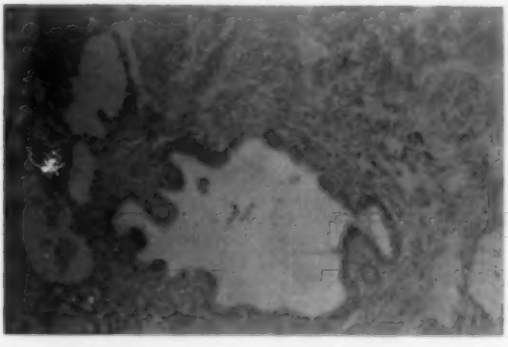
remained negative, persistently, on smear and culture. The patient responded quite well to medical management and in July, 1954, the patient was seen for the first time in surgical consultation. A review of the chest x-rays at that time revealed definite cavitary disease in the right apex, with numerous cystic areas at the left base. Bronchiectasis was suspected from a review of these films. Bronchographic studies on July 28, 1954, (Figure 2) revealed destruction of the right upper lobe and saccular bronchiectasis of the posterior basal segment of the right lower lobe. The left lower lobe was entirely bronchiectatic with large saccular dilatations seen and, also, a moderate amount of bronchiectasis of the inferior segment of the lingula. In review of the open cavity and the extensive bronchiectasis, it was felt that the patient's only hope for a satisfactory outcome would lie in bilateral excisional surgery. Since the cavitary lesion occupied the right chest, the right hemithorax was chosen for the first resectional surgery. On August 26, 1954, a right upper lobe lobectomy was performed without undue difficulty. The right upper lobe was atelectatic and several small air containing cysts were present. The lower lobe revealed, also, an area of atelectasis, corresponding to the bronchiectatic area as seen on the bronchogram. This area was removed with a segmental resection and the bronchi were noted to be extremely dilated, thin walled and cystic-like.

The patient tolerated the operative procedure well and the post-operative course was essentially smooth until September 8, 1954, (11th post-operative day) when the patient suddenly complained of severe left chest pain, followed by extreme dyspnea. Physical examination substantiated the initial impression of pneumothorax on the left side, which was subsequently proven by x-ray. The pneumothorax was of the tension type, as the patient became increasingly more dyspneic, and a closed intercostal drainage was instituted promptly. The patient responded well to this treatment and her dyspnea abated rapidly after deflation of the left



Dilated respiratory bronchiole showing a slightly folded mucosal lining of still ciliated columnar epithelium without goblet cells. The rest of the wall is composed of layers of collagenous tissue with some elastic fibers and interrupted circular layers of interlacing smooth muscle in which scant scattered lymphocytes are seen. The bronchus is surrounded by well aerated slightly congested alveolar parenchyma showing one small thin walled vein at six o'clock.

chest. However, the air leak persisted and was of such a magnitude that it was felt the leak would not close spontaneously, and also that the danger of empyema was now ever imminent. In spite of the short interval following the right resection, it was felt that resection on the left was indicated, more or less as an emergency procedure.

FIG. 1

FIG. 2

FIG. 3

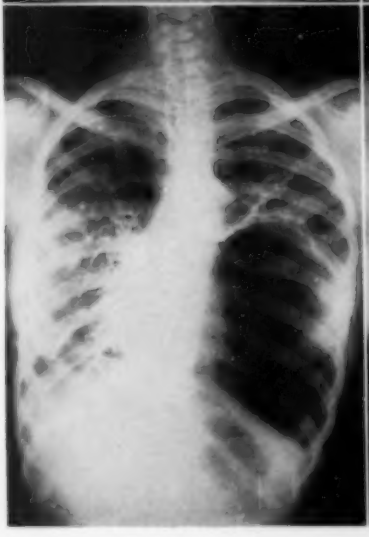


FIG. 4

Figure 1: Admission x-ray showing extensive bilateral disease.—*Figure 2:* Bronchogram revealing severe bronchiectasis of left lower lobe and lingula and the posterior basal segment of the right lower lobe.—*Figure 3:* Postoperative film after bilateral resectional surgery, showing large air containing space of left lung. Bronchogram reveals no evidence of bronchial communication.—*Figure 4:* Postoperative status after left chest intubation and deflation.

On September 10, 1954, (13th post-operative day) the patient had a left thoracotomy. Prior to undergoing anesthesia, the patient's left thoracotomy tube had been inadvertently clamped by personnel in the operating room, and the patient again developed a severe tension pneumothorax, became pulseless and the condition was critical until it was realized by the operating team what had taken place and the clamp was removed with rapid stabilization of the patient's condition. A left lower lobe lobectomy and lingulectomy was done, with removal of a ruptured, bronchiectatic lower lobe bronchus. After conclusion of the operative procedure and return to the recovery room, the patient's condition again deteriorated with a severe tachycardia and marked hypotension. The tachycardia responded to intravenous prostigmine and carotid sinus massage, with subsequent slowing of the pulse and gradual improvement in the overall general condition. After return to the ward, her condition remained satisfactory. The thoracotomy tubes were removed after 72 hours, when x-ray revealed complete expansion and no evidence of air leak was demonstrable. Her condition continued to improve. She remained afebrile and had no respiratory difficulty. However, on a routine chest film made January 5, 1955, there was seen a giant air containing space in the lower portion of the left chest, extending from the fourth rib, posteriorly, to the diaphragm. There had been no complaints by the patient of either pain or dyspnea, and we felt this air containing space had developed slowly, over a rather long period of time. The question was then raised as to whether we were dealing with a large air containing cyst or a localized pneumothorax. A bronchogram was made, which revealed no evidence of bronchial communication with this air containing space (Figure 3). A closed thoracotomy drainage was again instituted, with slow re-expansion of the lung. When pneumothorax could be demonstrated, after approximately 13 days, the thoracotomy tube was cut off flush with the skin and allowed to extrude spontaneously. The patient ran a low grade temperature during most of this time after insertion of the tube; however, she did not develop a frank empyema.

The subsequent course has been uneventful. Sputum remains negative on smear and culture. The patient has no complaints. She has gained in both height and weight. An early discharge is anticipated. X-ray findings are now satisfactory (Figure 4).

Histoplasmosis: Treatment of Two Cases with Beta-diethylaminoethyl Fencholate

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The antifungal agent, Beta-diethylaminoethyl fencholate has been demonstrated to inhibit the cultural growth of various fungi including Histoplasma capsulatum. Animals of several species have been subjected to acute and chronic toxicity studies with results that implied adequate safety to warrant clinical trial.[1]

The purpose of this report is to relate our recent experience with Beta-diethylaminoethyl fencholate in the treatment of two patients suffering from histoplasmosis. From Dr. Mackinnon Ellis, we first learned of this new drug, which he was employing in a case of histoplasmosis.[2] There has also been a report of its clinical trial by Michael and Vogel[3] who started the drug in their case several days after the development of clinical and radiographic improvement. They were unable to assess its usefulness.

Because of the relative paucity of cases of active histoplasmosis coming under the observation of any investigator and because the natural course of the disease is unknown, the evaluation of the usefulness of any drug in the treatment of histoplasmosis is difficult. Nevertheless, it is hoped that this report will contribute to an appraisal of the suitability of Beta-diethylaminoethyl fencholate in the treatment of histoplasmosis, and will stimulate further study by those who may encounter this uncommon disease.

Chronic Pulmonary Histoplasmosis

Case 1: R. No. 55019. A 63 year old white Tennessee farmer was first admitted to the Thayer Veterans Administration Hospital, Nashville, Tennessee on April 27, 1953. He had been well and working until the onset about three months previously of weakness, anorexia, slight nausea, night sweats, and chronic productive cough. His weight had dropped from 145 to 115 pounds. Extensive diagnostic studies failed to disclose any disease process. He was discharged May 22, 1953, unimproved, with nonspecific supportive medication.

On readmission February 26, 1954, his symptoms were essentially the same. His weight had not changed. His cough was productive of about 150 cc. sputum daily of which some 30-40 cc. were thick purulent secretions. On examination he appeared chronically ill, thin and tired. Dental status was poor. Auscultation of the chest disclosed moist medium-sized rales at the left apex posteriorly and rhonchi over both upper fields. The spleen and liver were not palpable. There was neither local nor generalized glandular adenopathy. There were no oral or lingual ulcers and the skin was not remarkable.

Initial laboratory findings were as follows: white blood cell count, 9,750; polymorphonuclear leukocytes, 80 per cent, lymphocytes, 19 per cent, eosinophils, 1 per cent. Sedimentation rate 34 mm. in 1 hour (Wintrobe corrected). Hematocrit was 41 mm. The urine concentrated to a specific gravity of 1.021; albumin and sugar were not present; microscopic examination was negative. Serum proteins were 6.6 grams per cent with

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albumin and globulin each being 3.3 grams per cent. In early March, 1954, skin tests to tuberculin (PPD Nos. 1 and 2) and to blastomycin undiluted* were negative. A barely positive reaction to coccidioidin, 1:100* and a positive reaction, measuring 10 mm. induration and 12 mm. erythema, to histoplasmin, 1:100,** were demonstrated. A second test with PPD No. 2 on March 15, was negative. Ten sputum smears and cultures were negative for acid fast bacilli. Two sputum cultures obtained March 22, and a third culture obtained March 24, were reported positive for Histoplasma capsulatum. Blood and bone marrow fungus cultures were negative. Bronchoscopic washings from the right and left upper lobe bronchi were negative on culture for fungi. The blood sera of March 25, and 30, showed a 1:16 reaction in the complement fixation test.

Chest roentgenograms (Figure 1A) on the previous admission of May, 1953, had shown only thickening of the pleura and several subpleural blebs at the right apex. By the second admission, March, 1954 (Figure 1B) there had developed bilateral infiltration interpreted as productive inflammatory disease extending from the apices to the second anterior interspace with linear strands radiating from the hilar regions to the apices. A radiolucent area at the right apex had persisted without change and on planographic study this appeared probably to be an emphysematous bleb.

Electrocardiogram showed occasional premature ventricular contractions and a first degree heart block, the P-R interval varying between 0.22 and 0.24 seconds.

His clinical course has been observed 13 months during which period there has been

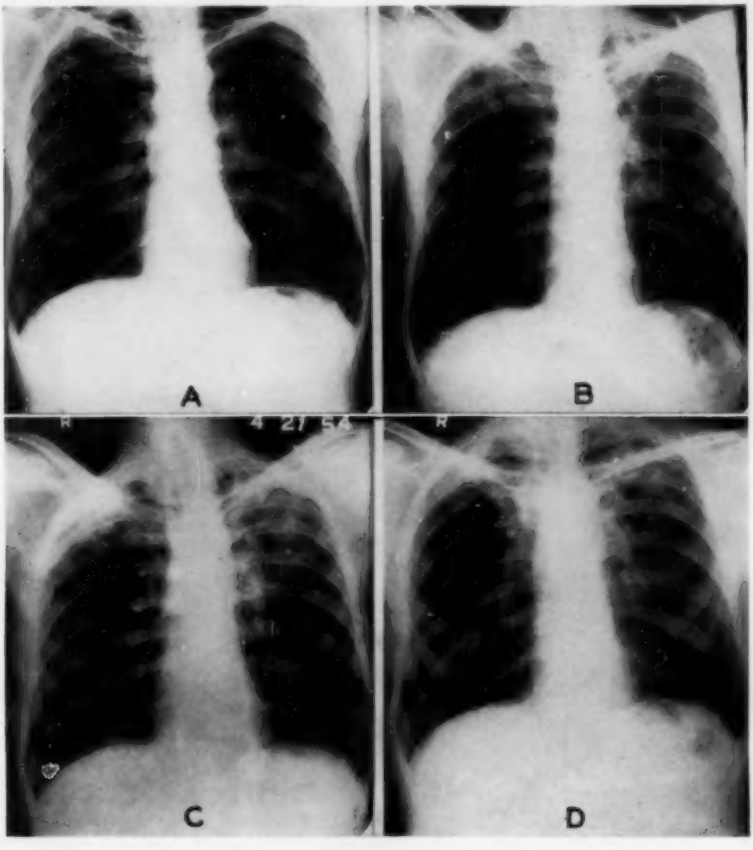

FIGURE 1

*Blastomycin was kindly supplied by Dr. David T. Smith, Durham, N. C.
*Coccidioidin was kindly supplied by Dr. Charles E. Smith, San Francisco, California.
**Histoplasmin, Eli Lilly.

both clinical and roentgenographic improvement. His treatment may be conveniently separated into three phases, consisting of three months of strict bed rest, two months of bed rest supplemented by treatment with Beta-diethylaminoethyl fencholate and eight months of gradually increasing activity.

Treatment during the first three months (March-May 1954) consisted of 23 hours rest in bed each day, a full diet, and general measures which included removal of all teeth for chronic gingivitis and peridontoclasia. His symptoms persisted and in addition he developed mild peripheral neuritis thought to be secondary to poor nutritional status. This slowly improved on a full diet with vitamin supplements. Night sweats gradually disappeared, but little improvement was noted in the anorexia, weakness, cough or weight. The chest roentgenogram of April 21 (Figure 1C) indicated increase of disease during the first two months but improvement was evidenced by the end of the third month, May 24 (Figure 1D).

During the next two months (June and July, 1954) his rest program was unaltered and he received Beta-diethylaminoethyl fencholate (MRD-112). This medication,* furnished in ampules containing 150 mg. of the drug in alcohol, was administered by diluting the contents of an ampule in 200 mls. physiological saline and infusing by slow intravenous drip once daily. The same anticubital vein was used each day with occasional exceptions for 60 days without encountering thrombosis or phlebitis. The clinical and roentgenographic evidence of improvement, which had started during the month (Figure 1D) prior to drug treatment, continued. Cough, sputum production and muscular aching decreased. Appetite improved. He gained weight from 115 to 126 pounds and remained afebrile. Chest roentgenogram of July 26 (Figure 2E) showed improvement evidenced by gradual regression and contraction of the densities in both apices.

The post medication period of eight months, August, 1954, through March, 1955, has been characterized by continued clinical and roentgenological improvement. He remained in the hospital until December, 1954, during which time he was allowed increased activity; resting two hours in the afternoon and nine hours at night. His appetite returned to normal, he gained an additional eight pounds, and his cough lessened. Considerable lassitude persisted.

He was then at home from January, 1955, until the present (April, 1955) during which time he spent eight hours daily in bed, eight hours in a chair, and eight hours doing light farm chores—milking a cow, feeding hogs and chickens. He noted an increase in energy, and a decrease in cough was significant, being productive of only 4 to 5 cc. of mucoid sputum daily. There was some decrease in appetite, however he stated he forced himself to eat, and he gained another two pounds.

Serial chest roentgenograms following completion of drugs showed the most marked regression of densities attributed to inflammatory infiltration in both upper lung fields through September 1, 1954 (Figure 2F) with gradual but steady clearing continuing through December, 1954 (Figure 2G) and March, 1955 (Figure 2H).

Repeated sputum cultures for Histoplasma capsulatum were consistently overgrown with contaminants which is the rule in our laboratory in the warmer months. Seven uncontaminated cultures were negative for fungus growth. Repeated smears and cultures of sputum were negative for acid fast bacilli. The monthly complement fixation antibodies varied little until November, 1954, when they declined to 1:2. In December, 1954, this test was recorded as negative; and in March, 1955, as 1:8. Complement fixation tests were done in the U. S. Public Health Laboratory, Chamblee, Ga. from March, 1954, through July, 1954, employing the technique of Schubert et al.[4]; in the Veterans Administration Area Reference Laboratory, Atlanta, Ga. in August and September, 1954, by the technique of Norden[5]; and subsequently at the Army Medical Center, Washington, D. C. by the technique described by Campbell et al.[6,7]

Toxicity studies, done before and after the use of Beta-diethylaminoethyl fencholate, consisting of clinical observation, hematological examinations, and renal and hepatic function tests, demonstrated no significant deviations from normal. The WBC, differential counts and hematocrit disclosed no hematopoetic alterations; urinalysis, NPN and PSP tests revealed no suggestion of renal irritation; bromsulphalein, cephalin flocculation, thymol turbidity, serum bilirubin, alkaline phosphatase and serum protein determinations remained normal.

Disseminated Histoplasmosis

Case 2: R. No. 48383. A 54 year old retired South Carolina truck farmer was referred to Thayer Veterans Administration Hospital in August, 1950, for further treatment of adenocarcinoma of the thyroid gland, for which a right hemithyroidectomy had been done elsewhere. He also had mild diabetes mellitus. Shortly after admission to this hospital total thyroidectomy was done. No local lymph node was found at

*Kindly supplied by the William S. Merrill Company, Cincinnati, Ohio.

operation. Microscopic sections of the excised thyroid gland showed evidence of malignancy. His postoperative course was uneventful and he returned home on a small dose of thyroid extract and 15 units of protamine zinc insulin daily. Subsequent examinations from 1950 to 1953 showed no evidence of recurrence or metastases.

He was readmitted in January, 1954, because of the discovery of two small nodules over the right sternoclavicular joint. A radical neck dissection and mediastinal exploration of January 18, 1954, revealed only two small lymph nodes which microscopically showed metastatic cancer. The postoperative course was stormy primarily because there developed around the tracheotomy tube a persistent infection which resulted in a superior mediastinal sinus tract which drained moderate amounts of serosanguinous fluid. By June, 1954, he had improved so he was ambulatory within the hospital.

In July, 1954, he became worse and thereafter pursued a steady downhill course. He developed septic fever reaching 102° F., ascites, mild jaundice, splenomegaly and hepatomegaly. A rash appeared, characterized by discrete, small tawny papules, located on the upper arms and the anterior and posterior aspects of the chest. The total white blood cell count was 2,000; with a differential showing 50 per cent polymorphonuclear leukocytes and 50 per cent lymphocytes. Biopsies of the bone marrow obtained from the iliac crest and of a dermal papule revealed intracellular yeast-like bodies morphologically typical of Histoplasma capsulatum.

On July 21, 1954, when he was critically ill, Beta-diethylaminoethyl fencholate, 150 mg. in 150 cc. physiological saline was given intravenously and this was repeated each day until July 26, the day of death. No improvement was apparent.

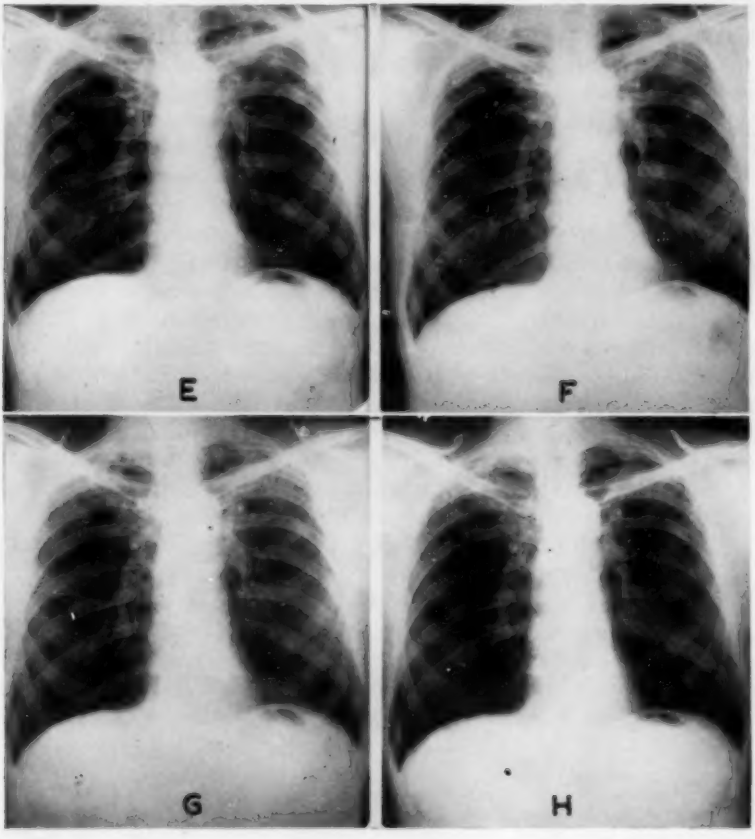

FIGURE 2

Laboratory studies just prior to therapy disclosed: white blood cells, 2,500; polymorphonuclear leukocytes, 79 per cent; lymphocytes, 21 per cent; hematocrit, 31 mm.; total serum proteins, 5.1 gm. per cent with albumin 3.0 gm. per cent and globulin 2.1 gm. per cent. The cephalin flocculation was 4 plus; thymol turbidity, 3.0. The indirect Van den Bergh was 1.2 mg. per cent and the total serum bilirubin, 2.2 mg. per cent. The NPN was 67 mg. per cent. Urinalysis showed a trace of albumin, 2-3 red blood cells, occasional white blood cells, and a few granular casts. On the day of death, the white blood cell count was 7,500 with 93 per cent polymorphonuclear leukocytes and 7 per cent lymphocytes.

Histoplasma capsulatum was cultured from specimens of blood and bone marrow obtained on July 21, and 22, respectively. The blood serum of July 23, gave a 1:128 complement fixation reaction for Histoplasma.

Post-mortem examination showed widespread disseminated histoplasmosis. The only evidence of adenocarcinoma was found in one mediastinal lymph node, in which there were also numerous organisms of histoplasmosis.

Discussion

Except for ethyl vanillate, which gave some encouraging results in a small group of patients studied by Christie and Peterson,[8] no drug of promise has so far been employed satisfactorily in the treatment of histoplasmosis. Beta-diethylaminoethyl fencholate is a new chemotherapeutic agent which we have tried in two cases of culturally proved histoplasmosis.

In the first patient with chronic pulmonary histoplasmosis, our observations do not conclusively demonstrate that this drug altered the course of the disease. There are a number of reasons why the evaluation is difficult. There is too little known about the natural course of pulmonary histoplasmosis to say that the illness of this patient was milder or shorter than the average. In this respect the problem is not like that in pulmonary tuberculosis where extensive clinical experience has established the natural course of untreated infection; yet even in tuberculosis, correct evaluation of specific antimicrobial agents has been difficult. Furthermore, bearing in mind that Johnson and Batson[9] noted a favorable response to bed rest and general measures in their case of pulmonary cavitary histoplasmosis, it is impossible to show to what extent his recovery was the result of bed rest and general therapeutic measures instead of specific drug effect. Clinical and roentgenographic improvement was evident prior to specific drug treatment. The gradual improvement continued during drug therapy and thereafter, both during the phase of bed rest and the period of rehabilitation. Nevertheless, the possibility exists that Beta-diethylaminoethyl fencholate did favorably affect his course. The dosage and duration of administration of the drug were selected arbitrarily and may not have been optimum.

In the second patient, it was evident that the few days of drug treatment did not alter the rapid downhill course of his disease. If this drug has any suppressive effect on histoplasmosis in the human, it was not sufficiently potent to influence this particularly overwhelming disseminated infection.

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Surgical Aspects of Pulmonary Blastomycosis With Report of Two Cases

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With the advent of greater safety in thoracic surgery, an increasing number of thoracotomies is furnishing diagnoses in more obscure pathological processes and is giving us a better concept of the clinical course taken by many diseases affecting the lung. Such is the case with pulmonary blastomycosis.

Prior to 1951, systemic and pulmonary blastomycosis was a formidable disease with a mortality rate of about 92 per cent.[1] Treatment with surgery, x-ray, and other physical and chemical preparations had been unsatisfactory. With the report in 1951 by Schoenbach of the efficacy of stilbamidine therapy for systemic blastomycosis, a great advance was made.[2] There still remains much room for improvement in therapy and knowledge of its clinical course. In 1954, White was able to collect only 13 previously reported cases of pulmonary blastomycosis which had been treated by resection;[3] to this he added four additional cases. Of the total series, only two had been diagnosed pre-operatively.

The following two case reports are added to the increasing number which are being recognized in an effort to improve our knowledge of this disease.

Case 1: A 36 year old caucasian male was admitted to Fitzsimons Army Hospital September 28, 1953, because of a pulmonary lesion first discovered on routine x-ray film in June 1953. This lesion had caused no symptom but, because no improvement was noted on follow-up films, it was thought that additional work-up was indicated. He had had 11 years of Army service with duty in the United States, the East Coast, and in Kansas where he had served two years prior to going to Formosa in 1951. Family history was non-contributory, but his past history was significant in that he had pneumonia in 1944 and mild diabetes mellitus, which could be controlled by diet alone.

Physical examination revealed a 200 pound man with normal pulse, blood pressure, and temperature. The chest, as well as the remainder of the examination, was within normal limits. Bronchoscopy demonstrated a normal bronchial tree. Bronchial washings were negative for acid fast bacilli and fungi.

Routine blood count and urinalysis were normal. X-ray film of the chest demonstrated an infiltrative process on the left which was well localized in the upper portion of the lingula (Figure 1). Serial films showed no change. PPD was 4 plus. Skin tests for histoplasmosis and coccidiodomycosis were negative but for blastomycosis a 2 plus test was obtained in 1 to 100 dilution.

Since neither malignancy nor obstructive pneumonitis in the lingula could be ruled out, exploratory thoracotomy was done on November 2, 1953. At surgery, the pleura was free of adhesions and all disease found was located deep in the lingula. There was no hilar lymphadenopathy. The lesion was firm and nodular. Segmental resection was performed, removing the lingula.

The histology of the lesion was typical for blastomycosis. Material removed for fungus culture grew a yeast-like, budding organism which was morphologically similar in all respects of blastomyces. The superior bronchus entered a 4.0 cm. necrotic granular mass (Figure 1) which was roughly spherical and was yellowish-brown. It contained several pockets with liquefaction. The mucosa of the bronchus adjacent to

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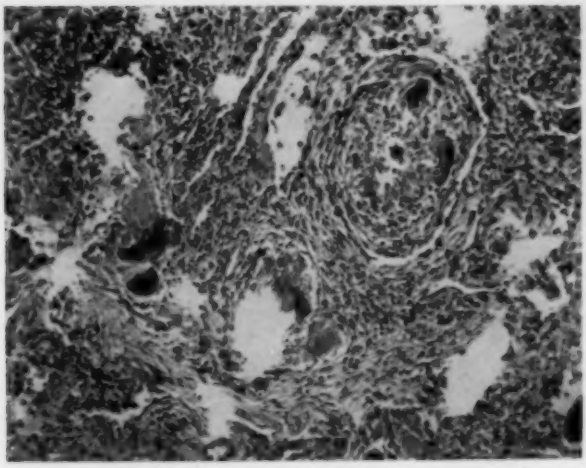

FIGURE 1 (Case 1): Histologic Section—Granulomatous Tissue.

the mass was ulcerated and replaced by large numbers of foreign body type giant cells, These contained numerous spherules of various sizes but approximately the size of a red blood cell. The spherules had a thick capsule with dark-staining granular material in the center. Some were in the budding stage.

His convalesence was uneventful. Post-operatively, he was placed on a 12 day course of stilbamidine, receiving 150 milligrams a day for a total of 1.8 grams. No complication followed this therapy, and he was discharged to duty with no pulmonary symptom and a clear chest x-ray film A follow-up report in March 1955, gave information that he had remained asymptomatic and was continuing to do full military duty.

FIGURE 2

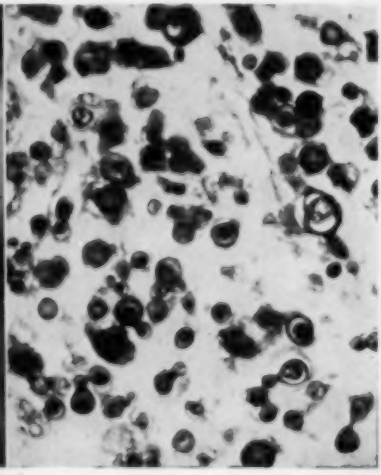

FIGURE 3

Figure 2 (Case 2): Pre-operative X-ray.—*Figure 3* (Case 2): Blastomyces removed from mouse.

Case 2: A 38 year old white man was transferred to Valley Forge Army Hospital January 21, 1955. He had been well until June 1954, when he noticed vague chest pain, fatigue, malaise, and shortness of breath. In August, he developed cough productive of small amounts of white sputum. This was studied for acid fast bacilli at the transferring hospital, but none was found. The reaction to PPD was 2 plus. His symptoms, except for right chest pain, gradually began to subside without specific therapy but, because chest x-ray film revealed a persistent lesion in the right lung field (Figure 2), he was transferred here.

His past history is significant in that he was hospitalized in an Army hospital in California in 1944 for similar complaints but chest x-ray film and sputum studies were negative. He had re-entered military service in 1948, served in Korea in 1950 and 1951, and after eight months' service in the United States, he was sent to Germany in 1952 where he remained until he was transferred to this hospital.

At the time of admission, he was afebrile and complained only of intermittent, pleuritic, right anterior chest pain. Physical examination, including the chest, was within normal limits. Routine laboratory studies were negative. Sputum smears and cultures were repeatedly negative for acid fast bacilli and fungi. Serial chest x-ray films showed a soft, unchanging density in the right lung field at the level of the second interspace anteriorly (Figure 2). Bronchoscopy revealed a normal endobronchial tree, and washings were negative for acid fast bacilli and fungi.

On April 6, 1955, right thoracotomy was done and an area of consolidation noted in the posterior segment of the right upper lobe. Posterior segmental resection, with a wedge removal of disease from the apical segment, was carried out. The post-operative course was uneventful. On smear and culture of the surgical specimen, typical blastomycosis was found. He was started on stilbamidine intravenously and continued on daily dosages of 150 milligrams until 1.8 grams had been given. No ill effects resulted from this medication. Skin test done post-operatively with blastomycosis antigen was negative. He was returned to limited duty for a period of six months, following which he is to return for follow-up. Figure 3 shows a photomicrograph of mouse injected from cultures.

Discussion

The two reported cases are similar in several respects—the clinical course of the disease, failure of pre-operative diagnostic attempts, and response to treatment. These two patients may have had excellent resistance to the disease and may represent either an early phase or a more smoldering form of blastomycosis which would have healed without therapy. They differ in this respect from the more advanced cases which have a fulminating course. Because they had well localized disease and possibly better resistance, it was thought a minimum amount of stilbamidine was adequate in order to prohibit post-operative spread of the fungus. The therapeutic dose usually recommended for cure in advanced cases was reduced since the only focus found had been removed and because the complication rate after large doses of stilbamidine therapy is high. Not only have toxic effects on the liver and kidneys been reported, but also trigeminal neuropathy in 70 per cent to 75 per cent of patients so treated.[4, 5] Further, the report by Buechner, et al,[6] of a patient with pulmonary blastomycosis who was cured by resection alone indicates that drug therapy is not always necessary.

Had these patients had the more fulminating form of the disease, or had a pre-operative diagnosis been made, they would have been treated by a full course of medical therapy in an attempt to circumvent surgery. This would seem the more logical plan of treatment. However, there is probably some analogy between blastomycosis and tuberculosis since both cause a destructive process with granulomatous changes. If this similarity also exists in response to drug treatment, resection may be an important

adjunct in selected cases. In each of our cases, however, pre-operative diagnosis could not be made. Thus, thoracotomy was felt justified for diagnosis as well as therapy. Unless the blastomyces can be recovered from the sputum or bronchial washings, or unless dermatological manifestations are present, it seems impossible to make a definitive diagnosis. The skin test, although helpful, is sometimes negative even in patients with acute blastomycosis. In an unproved case, a therapeutic trial of stilbamidine is unjustified as malignant lesions or other serious inflammatory processes are more common and would thus be neglected. It would seem also that the drug is too toxic to use without a diagnosis.

The first patient had been followed for 27 months without recurrence and with no complication from therapy. The second has only been followed for ten months, which is too early to rule out recurrence or complication; however, his progress to date has been excellent.

Since so few cases have been reported, it seems improper to recommend a single outline for therapy. Until more knowledge is obtained, each case should be judged on its individual characteristics and treated accordingly. We do not feel hesitant, however, in considering diagnostic thoracotomy an entirely justifiable procedure and an excellent means for control of disease when followed by post-operative stilbamidine therapy.

It is interesting from an epidemiological standpoint that the first patient left the United States in 1951 for the Far East. The lesion in his lung was noted on routine x-ray film in June 1953, at which time it caused no symptom. The second patient left the United States in 1952 for Germany, where he remained until symptoms began and x-ray film revealed the pulmonary lesion two years later in September 1954. These two cases, with the one reported by Matsumoto,[7] raise some doubt that this disease is limited to North America.

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Scopolamine-Methadon-Demerol Treatment of Emergency Status Asthmaticus

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There is perhaps no condition that better tests the therapeutic skill of the physician than chronic bronchial asthma. Yet sometimes, despite most skillful handling or through deficient cooperation on the part of the patient or even because of extraordinary circumstances, the apparent end of the road is an extreme status asthmaticus. The sight and the actuality are most alarming. The dusky plethoric or gray cyanosis of face and mucous membranes, the stridor of extreme air hunger, the weak rapid pulse are signs of emergency and may be prelude to death.

To combat this emergent abnormal state a number of therapeutic maneuvers have been recommended. Without entering into debate on the relative merits of the various therapeutic agents or their sequential recommended use we would like to detail a typical case history and outline a successful method of use of a combination of scopolamine with methadon given intravenously. We have not observed any mention in the literature of the use of these agents in this manner for this purpose. In other and more numerous cases meperidine (Demerol®) with equal benefit was used in place of methadon in the combination.

Case Report: R. S. age 44, housewife, had a history of hay fever of 30 years duration followed in the past three years by increasingly severe asthma with paroxysms of cough, only slightly productive of sputum. Previous intradermal testing was unsatisfactory because "almost all of the tests were positive." Antihistamines, aminophyllins, cortisone, iodides and climatic change previously had little effect on the frequency and duration of the paroxysms. The past history was otherwise not remarkable except for pleurisy 18 years ago and appendectomy and salpingectomy two years before she was first seen. There was history of asthma in the mother and two sisters, and eight other siblings had "allergies."

On physical examination when first seen, she was stocky, slightly cyanotic, weighed 170 pounds and had audible wheezing, labored breathing, some increased tympany on percussion of the chest, and bilateral moist rales and squeaks. Other findings were not abnormal except for a small uterine myoma. The blood count showed hemoglobin 91 per cent or 13 gms.; white blood cell 6600 per cubic mm.; erythrocytes 4.4 million per cubic mm.; Differential: Polymorphonuclear neutrophils 70; small lymphocytes 27; eosinophils 3. Sedimentation rate was 14 mm. in one hour. Urine was negative for albumin and sugar. X-ray film of the chest revealed no abnormality.

During the 48 hours after she was first seen ephedrine, epinephrine, penicillin, and mild sodium butisol sedation were ineffective. She was completely unresponsive to injections of epinephrine and suddenly her dyspnea became so aggravated and continuous that hospitalization was recommended. The sputum culture showed a predominance of pneumococci, Staphylococcus aureus, Neisseria catarrhalis, and Subtilis brevis. Antibiotics, mainly aureomycin and erythromycin, brought about improvement and bronchoscopy disclosed no abnormality. She improved and was discharged in three days.

From the Department of Medicine, University of California at Los Angeles and the Santa Monica Hospital.

Three weeks later on April 27, 1952, she again suddenly went into a most severe state of bronchospasm with almost continuous cough, dyspnea and cyanosis and was readmitted to the hospital. Her temperature was 99.2° F., pulse 110 and respiration 26. Parenteral epinephrine and aureomycin were ineffective. The condition in the next two days remained static on repeated instillations of paraldehyde 20 cc. per rectum and forced breathing with helium 10 per cent, oxygen 90 per cent. The pulse rate then rapidly rose to 140 and temperature to 101, axillary. Respiration rate ranged between 20 and 30 and cyanosis increased markedly so she was deemed in extremis and received last rites.

At this time a solution of 5 mgm. methadon Hcl and 1/100 gr. scopolamine in 1.5 cc. of water was prepared and of this solution 0.4 cc. was slowly given intravenously, about two minutes being required for the injection. With stethoscope on the chest one could hear the sibilant squeaks and expiratory wheeze rapidly disappear. She relaxed, became drowsy, and the cyanosis disappeared. For 24 hours these injections of 0.4 cc. each were repeated at approximately three hour intervals, keeping her in a semicomatose state and without asthmatic symptoms or signs. This was considered a heavy repetitive dosage, necessitated by the extreme gravity of the situation as well as this patient's high hypnotic threshold. Optimally half this dosage is generally considered adequate for single injections at four hour intervals. Next day she began taking food and liquid by mouth, and little of the injection was required. Epinephrine sensitivity returned. Her convalescence was rapid and five days later she left the hospital.

She was removed from a home which contributed external allergens in rugs, drapes, plants etc. to a severely furnished upper floor level apartment and was satisfactorily maintained on ACTH and antibiotics until advent of prednisolone. At present she is maintained on 12.5 mgm. of this oral steroid daily and carries on almost fully normal activity with but rare evidence of asthma.

COMMENT

To date the number of urgent cases upon which this treatment has been employed, largely by one of us (S.W.S.), has amounted to approximately 100 over the past 10 years. In the majority of these, 50 mgm. of meperidine replaced the usual 5 mgm. of methadon in the scopolamine mixture although the methadon has had in our experience an occasional advantage of being less likely to cause nausea. The spasmolytic action has been uniformly successful.

The range of dosage of the demerol-scopolamine has been variable but in only one instance has it been necessary to give more than 50 mgm. of demerol and 1/200 gr. of scopolamine at one time. Single injections often suffice. For example, one debilitated cyanotic patient who had productive cough with considerable respiratory effort, had bronchospasm due to bronchogenic carcinoma at the corina. Demerol alone at other times was ineffective but when she was given scopolamine 1/400 gr. and demerol 5 mgm. intravenously over a period of five minutes the high pitched sibilant rales as well as evidences of pulmonary edema disappeared within 20 minutes. In this case the demerol dosage was decreased because of debility. Her respiratory effort was markedly reduced and cyanosis disappeared. In this critically ill patient the small dose was adequate while a larger one might have been undesirable. By contrast an obese 54 year old man presenting asthmatic bilateral high pitched rales, labored expiratory wheeze and coughing spells, was maintained for a six hour period by a single intravenous injection of scopolamine 1/100 gr., demerol 50 mgm. given over a five minute period. His acuity of cerebration was moderately diminished as evidenced by slow speech response and there was some

amnesia. There was no respiratory depression. The sallow facies changed to normal pink coloration.

That the demerol-scopolamine combination action is equal to methadon-scopolamine is exemplified by the case of a 34 year old woman of average size who was originally brought to the hospital in a severe asthmatic state. She was unconscious, cyanotic and in a severe state of pulmonary edema. Minute doses of demerol and scopolamine, 12 mgm. and 1/400 gr. respectively, were given slowly by vein at approximately five hour intervals acccompanied by the use of oxygen with mild positive pressure given manually by means of an anesthetic machine. Consciousness returned after about three hours. Her condition then improved rapidly. The medication was no longer required after 24 hours. She was brought to the hospital on two subsequent occasions in a similar condition with similar treatment and with favorable results. A few months later another attack began while she was in an ambulance being taken to desert terrain away from allergens. En route her condition became rapidly worse and she died soon after her arrival at her destination. The demerol-scopolamine was not given in this final emergency. At the time death occurred she was under other medical supervision.

Judgment is required at time of injection so that the quantity given is enough to cause relaxation yet not so much as to result in profound depression or mental aberration. An average individual would be treated by injection of a small fraction of a solution of 1/5 cc. containing 5 mgm. methadon and 1/100 gr. scopolamine, or of a solution of 2 cc. containing 50 mgm. demerol and 1/100 gr. scopolamine given slowly intravenously with the stethoscope on the chest so that the injection may be stopped with onset of bronchial relaxation. Thereafter increments are given according to best judgment as to time and quantity of solution, being careful never to give more than necessary for broncholytic effect, but without respiratory depression.

It should be noted that although morphine is known to cause bronchial constriction and is generally interdicted for asthmatic patients this interdiction on the contrary does not hold with proper dosage for the synthetic agents meperidine and methadon nor for scopolamine,[1] which also relaxes bronchi. The spasmolytic site of action of the scopolamine appears to be both cerebral and vagal with probable anterior hypothalamic effect as well. The hallucinatory side effects of scopolamine may be encountered but do not weigh in the balance in the cases of emergency requiring resort to the scopolamine-meperidine-methadon combinations. Milder degrees of status asthmaticus do not require these drugs but may respond,[2] as in the above case report, to corticotrophins.

REFERENCES

1 Adriani, J.: *The Pharmacology of Anesthetic Drugs*, Springfield, Illinois, Charles C Thomas, publisher. 3rd Ed., 1952.

2 Ball, K.: "Severe Asthma Treated with Corticotrophin," *Lancet*, 266:1162, 1954.

Catheter Migration from Uterus to Lung, Perforating the Diaphragm

A CASE REPORT

MARY M. POWELL, M.D.
Baltimore, Maryland

A young, white woman with symptoms suggestive of lung abscess was found at thoracotomy to have a catheter in the left chest. This unsuspected foreign body extended from below the diaphragm to the left upper lobe. Subsequently, a history of a criminal abortion one year previously was elicited. On re-examination of the pre-operative chest x-ray films, a linear radiolucent shadow representing air within the non-opaque catheter was visible.

This case is reported because of its rarity, and because of the unusual x-ray features. No similar cases of catheter migration have been encountered by the author in searching the literature. However, Dr. Walter Colbert stated that a similar case occurred several years ago at Charity Hospital in Louisiana, without any radiographic evidence of the presence of the catheter.

Case Report

S. T. a 31 year old divorced white woman was admitted to the Johns Hopkins Hospital on March 23, 1954, with the chief complaints of cough and feverishness of four months duration. A chest x-ray film done shortly after the onset of symptoms was said to have shown a "spot" on her lung, and several sputum examinations had been negative for tubercle bacilli. For three weeks, she had coughed up copious amounts of foul-smelling blood streaked sputum. There was also pain in the left chest, easy fatigability, and a weight loss of nine pounds.

On physical examination, she was a well developed and well nourished pale young woman appearing acutely and chronically ill. Her temperature was 99° F. and the pulse was 100. There was marked clubbing of the fingers. Examination of the chest revealed decreased breath sounds and medium moist rales at the left base. Splinting of the left chest was evident. Laboratory studies revealed anemia with a hematocrit of 23 per cent; the white blood count was 10,000. Sputum cultures were negative for tubercle bacilli and for fungi, but grew a Coli aerogenes. The tuberculin skin test was positive 1:10,000.

Chest x-ray films were interpreted as showing inflammatory changes in the left lung base. Bronchography showed no evidence of bronchiectasis or other abnormalities.

Several attempts at thoracentesis failed to obtain fluid from the left chest. Bronchoscopy revealed hyperemia of the entire tracheobronchial tree and purulent discharge from the bronchi of both lower lobes.

With the tentative diagnosis of "chronic lung abscess," penicillin and terramycin were given. Because of poor response to the antibiotics after five weeks, left postero-lateral thoracotomy was done. The left lower lobe appeared normal, but a mass was found extending from the lingula up to the left hilum along the periphery of the lung and measuring about 5 cm. in width. On dissecting the mass, it was found to contain a woven silk catheter which extended down through the diaphragm for a depth of 4-5 cm. It was about 12 inches long and was encrusted. Its presence within

From the Radiology Department, The Johns Hopkins Hospital.

the left chest was probably of many months duration. Because of the inflammatory induration of the left upper lobe, left upper lobectomy was done.

On further questioning her post-operatively, it was revealed that she had undergone a criminal abortion one year prior to admission. At that time, the operator had inserted a catheter into the uterus with a string attached. She was told to pull out the catheter by the string in 24 hours, and she did this. There may have been two catheters used during the procedure, however, one of which was not recovered. Following this, she aborted and was hospitalized. Eight days later, she was re-admitted with profuse vaginal discharge and bleeding, marked abdominal tenderness, and a palpable mass in the right lower quadrant. She was treated conservatively and discharged with the impression of resolving endometritis. Perhaps this episode was due to perforation of the uterus by the catheter with secondary pelvic peritonitis.

The chest x-ray films in retrospect clearly reveal the radiolucent shadow of the catheter in the left lower chest, extending below the left diaphragm and surrounded by inflammatory infiltrations.

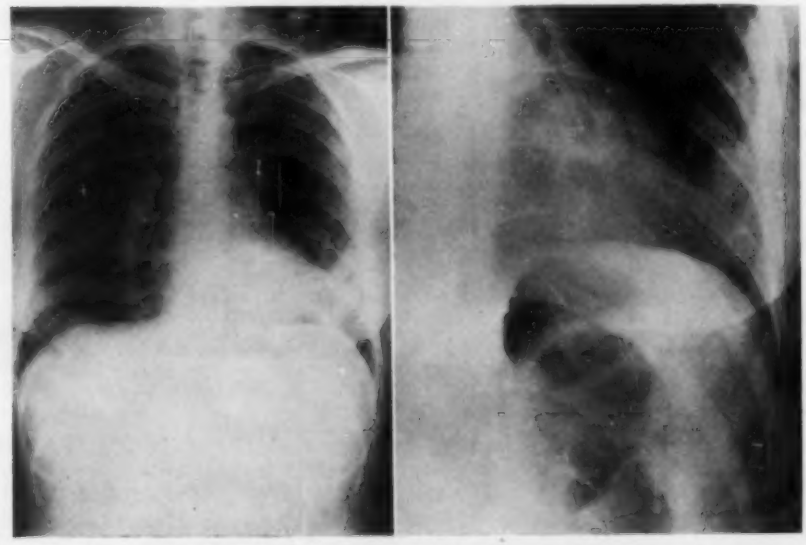

FIGURE 1A FIGURE 1B

Figure 1A: P.A. film of the chest shows chronic inflammatory infiltrations in the left lung base.—*Figure 1B:* Magnified view of the left lung base shows the linear radiolucent shadow of the catheter lumen extending vertically from the left upper quadrant through the diaphragm into the left lung.

Report of the Committee on Non-Surgical Therapy

I. The "Ten Cases" were studied in Britain by Dr. C. W. L. Jeanes and Dr. R. R. Trail, with one hundred physicians participating. A summary of this study is to be presented to the Canadian Tuberculosis Association at the 1956 meeting by Dr. Jeanes. Our Committee furnished them with x-rays and questionnaires for their study so the analysis of their opinions could be compared with our study (published in the January, 1955 issue of *Diseases of the Chest*). This same study was also done in Germany last year by Dr. Peter-Paul Schneider and Dr. med. habil. L. Rickmann, with one hundred German physicians participating, and is available for comparison.

John E. Rayl and James D. Murphy, of the Veterans Administration Hospital, Oteen, North Carolina, used this same technique for a paper on a Large-scale Jury Type of Review of the Indications for Surgery in Pulmonary Tuberculosis, which was published in the February, 1956 issue of *The American Review of Tuberculosis and Pulmonary Diseases*. Credit was given to us for developing the technique.

II. The problem of the known recent converter to tuberculin was discussed at our Committee meeting in Atlantic City in June, 1955, and a preliminary report was presented to the Board of Regents of the College in Boston on November 27, 1955.

As a result of those discussions, the Committee decided that a more formal study should be embarked on. To that end, the Committee members were canvassed by questionnaire. There were 22 replies out of a possible 25. These were analyzed with the following results.

1) *Definition*: Any known recent converter to tuberculin without demonstrable x-ray evidence of pulmonary tuberculosis or other known tuberculous lesions, such as cervical glands, etc.

Twenty-one of the men agreed with this definition. The one disagreeing stated, "A recent converter may or may not have other demonstrable evidence of active tuberculosis." This was not the intent of the Committee in defining a recent converter.

2) In such converters, gastric wash or tracheal lavage should be done. These washings should be examined by culture and/or guinea pig inoculation, or both.

Seventeen agreed and five disagreed. Those who disagreed stated as follows:

"Recent converters, having no demonstrable x-ray evidence of pulmonary tuberculosis, would have no way for the tubercle bacilli to get into the stomach or bronchial tree."

"I feel observation is adequate."

"Unless the converter is under three years of age."

Presented before the Board of Regents, 22nd Annual Meeting, American College of Chest Physicians, Chicago, Illinois, June 7, 1956.

"Not feasible for general use. OK for special cases."

One disagreed, making no comment.

3) It becomes necessary to define a test dose of tuberculin. One tuberculin unit is defined as 0.00002 mg. reference standard PPD (Purified Protein Derivative) or 0.01 mg. international standard OT (Old Tuberculin). The test dose of intradermal tuberculin for defining a converter should be:

a. Five tuberculin units—0.0001 mg. PPD or 0.05 mg. OT.
b. Ten tuberculin units—0.0002 mg. or 0.1 mg. OT.
c. Some other dose (please specify).

Eleven men indicated 5 tuberculin units, and ten indicated 10 tuberculin units, while one specified 100 tuberculin units.

It would seem that in the minds of these men there probably is not enough difference between 5 and 10 tuberculin units to make much difference in their opinion. This is what is actually shown in their answers. The old method commonly used in tuberculin testing was to first use 0.01 mg. OT and then jump to 1.0 mg. OT which, of course, is a marked difference—100 times as much. Or a comparable dose of PPD was used. In Palmer's analysis of reaction to tuberculin around the world, he states that 5 tuberculin units is the dividing line between infection and no infection, except in the United States where 10 tuberculin units can be taken as the dividing line—leaving out certain portions of the Southeast where 5 units would be a better level.

4) We would do *only* a single test with the previously specified dose.
8 replied affirmatively to this.

If negative, we would repeat this test with a stronger dose (specify the dose) to divide a reactor from a non-reactor to tuberculin.
14 replied affirmatively to this.

Of the 8 doing only a single test, 5 would use 10 tuberculin units, and 3 would use 5 tuberculin units.

Of the 14 repeating the test: 4 would use 250 tuberculin units, or 0.005 mg. PPD; 3 would use 100 tuberculin units; 2 would use 0.1 mg. OT, or 10 tuberculin units; 2 would use a stronger dose than 10 tuberculin units, the exact dose not specified; and 3 stronger than 5 tuberculin units, not specifying the exact dose.

There seemed to be a strong leaning toward repeating the test with a stronger dose on an initial non-reactor, before saying definitely that an individual was a non-reactor to tuberculin.

5) We need to define the time of a "recent" tuberculin conversion.

a. For adults:
20 agreed with the previous definition, which was "within the period of one calender year."
2 disagreed—setting the time at six months.

b. For children under the age of four:
20 agreed that it was assumed that the infection was "recent."
2 disagreed—setting the age limit at two years.

Two men commented that, in routine tuberculin testing, if the tests were performed every six months the recent converter would be more readily detected.

6) Which known converters need treatment?

a. Under four years of age:

16 would treat each converter under four years of age.

6 would do otherwise—2 treating those under two years of age, and 3 would give no treatment at any age but would recommend observation only.

b. Other ages, that is, over the age of four years:

6 would treat such converters under conditions of ordinary exposures.

15 would not treat such converters, but would observe only.

1 did not give direct answer—made comment.

Comments under this section:

"Some should be given isoniazid (prophylactic therapy). At present the intention of the examination must determine which cases." This does not reflect a clear understanding of the first definition.

One physician would "keep antibiotics for time of definite disease." This does not agree with the opinion that recent known conversion is the beginning of the disease tuberculosis.

7) At *any* age where there is a known heavy recent exposure, treatment of a recent converter is recommended.

13 agreed.

9 disagreed. Of these, 4 would treat if the converter was under 20 years of age, and one if under four years of age.

Comments under this section:

"Would observe only—with the exception of those persons apt to be lost to follow-up."

"Do not think you can measure probability of having progressive disease in a converter based on exposure to infection."

One physician wanted to wait for a controlled and long-term (5 to 20 years) follow-up before treating *all* converters.

8) Method of treatment of recent converters:

12 would use INH alone, in a dosage of 5 mg. per kilo—11 of these for one year, and one for six months.
Correlating this with the previous answers, they apparently had in mind mainly the treatment of children under the age of four years.

3 would use INH alone, in some other dosage—3 to 10 mg. per kilo for one year.
This makes 15 out of 22 who would use INH alone, which is statistically significant.

6 would use INH with PAS, for a general average of one year.
1 specified INH with streptomycin, "in massive dosage for six months."

Tuberculin Testing or BCG

1. The Committee recommended that, in areas with a high incidence of infection, prophylactic vaccination of non-reactors with BCG would be the method of choice.

18 agreed.
4 disagreed.

Comments:

Of those agreeing, one would use BCG "until the efficacy of of INH is established or not as a prophylactic measure."
Of those disagreeing, two stated that "BCG is not the method of choice. The problem is not among the negatives but among the positives who will develop disease."
Among those disagreeing, one physician stated, "BCG vaccination ignores the principles of detection and eradication of tuberculosis—its value is limited and its effectiveness questionable."

2. In areas with a low incidence of infection, routine tuberculin testing with treatment of the known recent converters would be preferable.

18 agreed.
3 disagreed.
1 did not answer this question.

Comments:

Of those agreeing, one stated that routine tuberculin testing should also be done in areas of high incidence of infection.
One agreed "provided an adequate program of case-finding and isolation of positive cases was part of the program."
Of those disagreeing, one physician would recommend BCG. Another considered "routine tuberculin testing and BCG both impractical in low incidence areas."

Committee on Non-Surgical Therapy
American College of Chest Physicians

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Alexander Libow, Miami Beach, Florida, *Vice-Chairman*
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Giles Wolverton, Dayton, Ohio

INTERIM SESSION

The Interim Session of the American College of Chest Physicians will be held at the Benjamin Franklin Hotel, Seattle, Washington, on November 25 and 26. An excellent scientific program, sponsored by the Pacific Northwest Chapter of the College, will be presented on Sunday, November 25. The program will include the presentation of twelve papers concerned with various aspects of heart and lung disease, both medical and surgical, a chest disease conference with a panel of experts to answer questions from the floor, three round table luncheon discussions and, in the evening session, nine Fireside Conferences on subjects of interest to the College membership. The preliminary program was published in the October issue of *Diseases of the Chest.*

The Ladies Entertainment Committee, under the chairmanship of Mrs. Frederick A. Slyfield, has arranged a tea and theater party for the ladies on Sunday, November 25. The tea will be held at 2:00 p.m. at the home of Dr. and Mrs. Franklin R. Smith in Seattle.

A cocktail party and banquet will also be held on Sunday, November 25, for the attending physicians and their wives, to be followed by the Fireside Conferences. All members and other interested physicians are cordially invited to attend this all-day session in Seattle on November 25. For additional copies of the final program and order forms for the luncheons and dinner, please write the Executive Offices of the College in Chicago.

Examinations for Fellowship in the College will be conducted on Saturday, November 24, and on Monday, November 26, the Executive Council, Board of Regents and Board of Governors of the College will hold their semi-annual meetings.

The Clinical Meeting of the American Medical Association will take place in Seattle, November 27 through 30, 1956.

SCIENTIFIC PROGRAM COMMITTEE REQUESTS ABSTRACTS FOR 1957 MEETING

The 23rd Annual Meeting of the American College of Chest Physicians will be held at the Hotel Commodore, New York City, May 29 through June 2, 1957. Plans for the scientific program to be presented at this meeting are under way. Emphasis will be placed on papers dealing with new and original research and investigation. One feature of the program will be a session devoted solely to a series of such papers limited to ten minutes for each presentation.

The committee urges those wishing to present papers to submit a 200-word abstract to Dr. Karl H. Pfuetze, Chairman, Committee on Scientific Program, 1919 West Taylor Street, Chicago, Illinois, before December 1, 1956.

MOTION PICTURE DATA REQUESTED

The Committee on Motion Pictures of the College is interested in learning of new motion pictures concerning diseases of the chest (heart and/or lungs). Physicians are invited to send their films for review by the committee and those approved will be listed in the directory of films now under preparation. Consideration is being given for films to be shown at the 23rd Annual Meeting of the American College of Chest Physicians to be held in New York City, May 29-June 2, 1957. Film data forms will be forwarded upon request to physicians interested in presenting their films at the annual meeting.

Please address films and inquiries to Dr. Paul H. Holinger, Chairman, Committee on Motion Pictures, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

College Chapter News

NEW ENGLAND STATES CHAPTER

At a meeting at the New England Deaconess Hospital, Boston on September 19, members of the New England States Chapter elected the following new officers:

President:	Frank G. Seldon, Manchester, New Hampshire
Vice-President:	Joseph N. Corsello, Providence, Rhode Island
Secretary-Treasurer:	S. Clive Cohen, Boston, Massachusetts

NORTHERN SOUTH AFRICA CHAPTER

The Northern Chapter of South Africa held its annual meeting and dinner in Johannesburg on May 22. Following the dinner, Dr. Albert Rabinowitz, retiring President, presented the annual report and spoke on the aims and objectives of the College. The following officers were elected:

President:	David I. Adler, Johannesburg
Vice-President:	Walter S. Linton, Transvaal
Secretary-Treasurer:	Denis N. Fuller, Johannesburg (re-elected)

Following the business meeting, Dr. Rabinowitz spoke on "Differential Diagnosis of Chest Pain."

This meeting was the fourth scientific session presented by the chapter this year. Speakers at past meetings were Dr. James Murray of the South African Institute for Medical Research, Mr. T. Holmes Sellors, Thoracic Surgeon of Middlesex Hospital, and Dr. Ian Webster, of the South African Institute for Medical Research.

MIDDLE EAST CHAPTER

The Second Annual Congress of the Middle East Chapter was held at the Hotel Ambassador, Bhamdoun, Lebanon, August 10-12. Physicians from Lebanon, Syria, Bahrein, Jordan, Pakistan, and Egypt attended the meeting. Among those present were the Director of the Ministry of Health of Lebanon, the President of the Lebanese Medical Society, the President of the Lebanese-French Medical Society, the President of the Lebanese Anti-tuberculosis League, the Dean of Tuberculosis Physicians of Lebanon, and representatives of the Dean of the Faculty of Medicine of the American University of Beirut, the World Health Association, the Damascus Faculty of Medicine and several physicians representing UNRWA.

During the opening session, at which the Minister of Health of Lebanon presided, Dr. Philip Chedid, President of the Lebanese Medical Society, and Dr. Elias Khoury, Dean of Chest Physicians in Lebanon, addressed the congress and Dr. Cesar Chehab, President of the Middle East Chapter, welcomed the physicians attending the congress. The following two-day program was presented:

"Importance of Early Diagnosis in Tuberculosis"
Basil L. Papanicolaou, Athens, Greece
"The Future of the Fight Against Tuberculosis in the Middle East"
B. Azmeh
"BCG"
Papken S. Mugrditchian, Beirut, Lebanon
"Methods and Environmental Aspects in the Prophylaxis of Pulmonary Tuberculosis"
Hector C. Nahas, Washington, D. C.
"Possibilities of Rehabilitation in Tuberculosis in Lebanon"
E. Dahan, Bhannes, Lebanon
"The Dispensary in the Fight Against Tuberculosis"
N. Naasan
"Tuberculosis Morbidity in Lebanon"
Edward Barouky, Bhannes, Lebanon
"ACTH and Tuberculosis"
A. K. Farra
"Sequelae in Pleuro-pulmonary Tuberculosis"
M. B. Khoury, Beirut, Lebanon
"Further Observations in the Treatment of Bronchial Asthma with Intravenous Novocaine and Respiratory Exercises"
R. Fares, Jordan

Panel Discussion—"Indication for Resection in Tuberculosis"
Moderator: John Long Wilson, Beirut, Lebanon
Panel: M. Mahassen, Charles K. Nucho, and E. Sader, Beirut, Lebanon

The following officers were elected:

President:	Edward Barouky, Bhannes, Lebanon
Vice-President:	Bechir Azme, Damascus, Syria
Secretary-Treasurer:	Wagih K. Sabbagh, Beit Mery, Lebanon

XI PAN AMERICAN CONGRESS (ULAST) MEDELLIN, COLOMBIA

The XI Pan American Congress of the Union of Latin American Tuberculosis Societies will be held in Medellin, Colombia, April 28-May 3, 1957. Requests for places on the program must be received prior to December 31, 1956. Physicians who are interested in presenting papers at this congress should address their letters as follows:

Secretaria del XI Congreso de la ULAST
Facultad de Medicina, Ofna. No. 10
Medellin, Colombia

Dr. Rafael J. Mejia C., Governor of the American College of Chest Physicians for Colombia, is President of the congress, and Dr. Carlos Arboleda Diaz, Regent, is the Vice-President. Dr. Fernando D. Gomez, Regent of the College for Uruguay, serves as the Secretary-General of ULAST.

Members of the American College of Chest Physicians who plan to attend this congress should also notify the Executive Offices of the College in Chicago.

College News Notes

Dr. Robert J. Anderson has been appointed Chief of the Public Health Service Communicable Disease Center in Atlanta, Georgia. Dr. Anderson formerly served as Medical Director and Assistant Chief of the Division of Special Health Services, Public Health Service, Washington, D. C.

Dr. N. E. Reich gave an address on August 14 before the faculty and members of the Research Institute of the Academy of Medical Sciences in Moscow, Russia.

Dr. William E. Adams, Chicago, Illinois, is currently at the University of Glasgow, Scotland, as guest lecturer.

ANNOUNCEMENT

The 14th Annual Course in Thoracic Pathology will be presented during the first two weeks of December, 1956 at the Hospitals de la Santa Cruz and San Pablo de Barcelona in Barcelona, Spain. This course is organized by Dr. Jose Cornudella, President of the Barcelona Chapter of the College, in collaboration with the heads of the cardiovascular and pulmonary departments of the two hospitals and the Faculty of Medicine of the University of Barcelona. The tuition for the course is 1,000 pesetas and all interested physicians should contact Dr. Cornudella for complete information.

Obituary

AMADEO VICENTE-MASTELLARI
1907-1956

Dr. Amadeo Vicente-Mastellari, a Fellow of the American College of Chest Physicians and Regent of the College for Central America, died on September 9 in Panama City, Republic of Panama. At the time of his death, Dr. Mastellari was Chief of the Chest Service of Gorgas Hospital, Professor of Phthisiology, National University of Medicine of the Republic of Panama, and Director of the Anti-Tuberculosis Campaign of the Republic of Panama. Dr. Mastellari, a graduate of George Washington University School of Medicine, Washington, D. C., was well known throughout Central and South America for his work in tuberculosis.

Dr. Mastellari was an Honorary Member of the Venezuelan Tuberculosis Society, the Guatemalan Tuberculosis Society, the Mexican Society of Tuberculosis, and the Tuberculosis Society of Cordoba, Argentina. He was Technical Advisor in Tuberculosis of the Inter-American Public Health Service, Republic of Panama, and President of the Central American Tuberculosis Society.

He is survived by his wife Essie, two sons and a daughter, and his mother.

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A.C.P. RECEIVES RESEARCH GRANT

A research grant of $43,100,000 has been awarded the American College of Physicians for the period September 1, 1956 through August 31, 1957, by the Department of Health, Education and Welfare of the Public Health Service in furtherance of its project to evaluate internal medicine in hospitals. The project was initiated in early 1956 by the College's Committee on Criteria for Hospital Accreditation under the chairmanship of Dr. Arthur R. Colwell, Sr., of Chicago. Dr. Marion A. Blankenhorn, Cincinnati, will direct the study.

The primary objective is the appraisal of medical care, and in addition, information will be gathered regarding internships and residencies in medicine where such programs exist. Close liaison will be maintained with the Council on Medical Education and Hospitals of the American Medical Association and appropriate committees in the Association of American Medical Colleges. The committee does not suggest that this pilot study shall substitute for any part of the present programs of the Joint Commission on Accreditation of Hospitals or the Council on Medical Education and Hospitals of the AMA, but will proceed parallel to the existing programs of both, probably leading to some revision in their internal medicine policies in the future.

COURSE IN LABORATORY METHODS

In cooperation with the Division of Special Health Services, Public Health Service, the Bacteriology Laboratories of the Communicable Disease Center, Chamblee, Georgia will offer a course in Laboratory Methods in the Diagnosis of Tuberculosis during January 21-February 1, 1957. This course is open to all grades of employed laboratory personnel who are approved by their state health officers. Laboratory directors and senior laboratory staff members may also make application for this course. Practical laboratory training in all phases of tuberculosis bacteriology, including preparation of culture media, microscopy, cultural procedures, diagnostic use of animals, and testing of drug sensitivity will be included in the course.

No tuition or laboratory fees are charged. Reservations should be made well in advance. Application forms may be obtained from Laboratory Training Services, Communicable Disease Center, Public Health Service, PO Box 185, Chamblee, Georgia.

RESIDENT FELLOW AVAILABLE

The Committee on Resident Fellowships of the College has recently approved the application of Dr. N., Colombo, Ceylon, who is interested in receiving one year's training in the medical aspects of heart and lung diseases. The candidate will be available in January, 1957 and will pay his transportation to this country. Dr. N. is 39 years of age, and graduated from the University of Ceylon Medical School in 1945. For further information, please write to the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

N.T.A. FELLOWSHIPS

The Medical Section of the National Tuberculosis Association, the American Trudeau Society, provides a limited number of fellowships to promote the training of clinicians, medical teachers, and scientific investigators in the field of tuberculosis. Awards are open to citizens of the United States for work within this country. Candidates holding the degrees M.D., Ph.D., or Sc.D., are eligible for awards. Studies may be oriented toward teaching or research. Residency in an approved hospital under such a fellowship will be credited by the American Board of Internal Medicine toward certification in internal medicine and pulmonary diseases. Predoctoral fellowships are also offered to graduate students who hold a bachelor's degree and who are working on a research project for an advanced degree other than M.D.

Further particulars concerning fellowships may be obtained from The Director of Medical Education, American Trudeau Society, c/o The Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia 47, Pennsylvania.

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POSITION WANTED

F.C.C.P., 42 years of age, former medical director of a 225-bed sanatorium, 15 years' experience in all phases of chest disease, including tuberculosis, with ward experience, Illinois and Michigan licenses, seeks position as medical director. Teaching affiliation desired, but not essential. Prefer Midwest or South. Minor thoracic surgery. Please address inquiries to Box 287B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Medical Director wanted for 150-bed tuberculosis hospital in Seward, Alaska. Salary $15,000 per annum, plus maintenance. For details, write Paul W. Nelson, M.H.A., Administrator, or F. J. Phillips, M.D., F.A.C.S., Medical Director and Thoracic Surgeon, Seward Sanatorium, Bartlett, Alaska.

Assistant Medical Director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, a 100-bed county tuberculosis hospital with active medical, surgical, out-patient, and investigative programs. Salary determined by experience. Furnished house and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address: E. V. Bridge, M.D., Superintendent.

CALENDAR OF EVENTS

NATIONAL MEETINGS

Interim Session and Semi-Annual Meeting, Board of Regents
American College of Chest Physicians
Benjamin Franklin Hotel, Seattle, Washington, November 25-26, 1956

23rd Annual Meeting, American College of Chest Physicians
Commodore Hotel, New York City, May 29-June 2, 1957

POSTGRADUATE COURSES

Postgraduate Course on Diseases of the Chest
Nashville, Tennessee, January 14-18, 1957

Postgraduate Course on Diseases of the Chest
San Francisco, California, February 25-March 1, 1957

3rd Postgraduate Course on Diseases of the Chest
Jersey City, New Jersey, March 6, 13, 20, 27, 1957

CHAPTER MEETINGS

Pacific Northwest Chapter, Seattle, November 25, 1956

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Telephone Clayburn 8-4921

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C. Gerald Scarborough, M.D.

Visiting Medical Staff:
Harold Guyon Trimble, M.D., Oakland
Cabot Brown, M.D., San Francisco
J. Lloyd Eaton, M.D., Oakland
Gerald L. Crenshaw, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
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ANNOUNCEMENT

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[1]Dr. Samuel Phillips: *Calcium Benzoyl PAS*, Paper presented at 15th VA-Army-Navy Conference on Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956.

G. R. Underwood, M.D.
Medical Director

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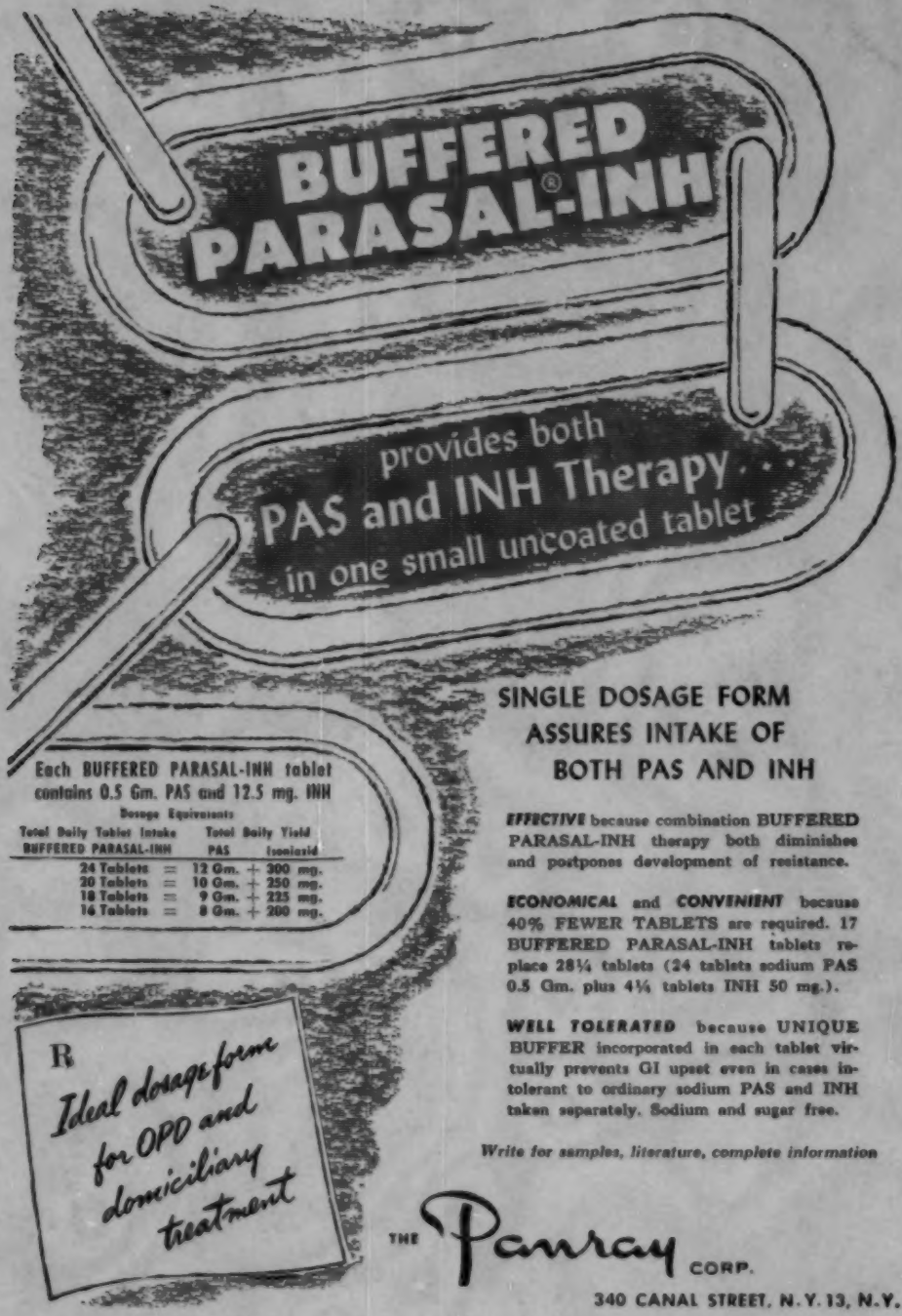
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